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The Effect of Virechana

Response to Novel Corona Virus

Highlights

Pharmacist in Patient Care

Natural Physical Factors and Integral

Discovering Thoughts, Inventing Future

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Contents of the Issue

i. Copyright Notice
ii. Editorial Board Members
iii. Chief Author and Dean
iv. Contents of the Issue

1. Gut Restricted Therapeutic Approaches to Inflammatory Bowel Disease. *1-10*
2. The Role of the Pharmacist in Patient Care (Book Review). *11-30*
3. Cytokine Storm: A Suicidal Immune Response to Novel Corona Virus. *31-37*
4. The Effect of Virechana with Manibhadra Churna in Psoriasis – A Case Study. *39-43*
5. Review on Effect of Vitamin C on Immune System. *45-50*
6. Leading Role of the Principles of Interaction between the Natural Physical Factors and Integral Organism in Medicine of the Future. *51-69*

v. Fellows
vi. Auxiliary Memberships
vii. Preferred Author Guidelines
viii. Index

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Gut Restricted Therapeutic Approaches to Inflammatory Bowel Disease

By Dr. Pranab Maiti & Dr. Rajiv Sharma

Department of Medicinal Chemistry

Abstract- Inflammatory Bowel Disease (IBD), consisting of Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic intestinal disorder that arises due to the damaged intestinal epithelium tissue, which most often leads to relapsing. Major treatment options range from dietary intervention at an early stage of the disease, to the use of steroids or anti- inflammatory drugs for most severe conditions. However, the side effects and associated comorbidities which bring disease recurrences points towards the unmet needs of the existing treatment options, which are limited to their non-holistic mechanistic functionality. Among them, many drugs work specifically by acting locally on the gut tissue, in other words at the site of the disease, both to exert maximal efficacy as well as to avoid undesired side effects. Here we have reviewed the recent interests in the gut restricted therapeutic approaches for new IBD therapies.

Keywords: IBD, UC therapies, CD therapies, gut-restricted compounds, colon-specific compounds, non-systemic compounds.

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Gut Restricted Therapeutic Approaches to Inflammatory Bowel Disease

Dr. Pranab Maiti [α] & Dr. Rajiv Sharma [σ]

Abstract- Inflammatory Bowel Disease (IBD), consisting of Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic intestinal disorder that arises due to the damaged intestinal epithelium tissue, which most often leads to relapsing. Major treatment options range from dietary intervention at an early stage of the disease, to the use of steroids or anti- inflammatory drugs for most severe conditions. However, the side effects and associated comorbidities which bring disease recurrences points towards the unmet needs of the existing treatment options, which are limited to their non-holistic mechanistic functionality. Among them, many drugs work specifically by acting locally on the gut tissue, in other words at the site of the disease, both to exert maximal efficacy as well as to avoid undesired side effects. Here we have reviewed the recent interests in the gut restricted therapeutic approaches for new IBD therapies.

Keywords: IBD, UC therapies, CD therapies, gut-restricted compounds, colon-specific compounds, non-systemic compounds.

I. Introduction

IBD is a chronic disorder of the gastrointestinal tract affecting severely the normal lifestyle of an individual. IBD comprises of CD and UC. While CD is characterized as epithelial damage throughout the intestinal tract from mouth to anus with multiple patches here and there in terms of their heterogeneous nature, morphology, and size; UC is more restricted to the damage of the colonic epithelia with a leaky gut localized mainly from cecum to rectum [1, 2]. Today approximately 10 million people are living with IBD in different parts of the world in addition to many which are underreported or undiagnosed due to the nature of the complexity of the disease [3].

At present, there is no real ready-to-use non-invasive easy diagnostic tool available for a quick assessment of CD or UC. In recent times, the disease prevalence is growing at a faster rate due to the widespread use of modern food habits (western diet), environmental factors and genetic make us; which might soon take an epidemic form of thedisease [4].

UC is the major component of IBD with clinical symptoms of chronic abdominal pain, diarrhea, bloody stool, fever, and weight loss. In general, people with a stomach infection has a higher risk of developing UC, but chronic life habits and conditions like smoking, high sugar or high-fat diet, and even anti-inflammatory or heavy antibiotic therapies are also the causes of developing UC [5]. Many patients develop colon cancer from UC. CD has a high prevalence from teenage group children to about 30 years old adults [6].

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II. IBD Causes and Factors

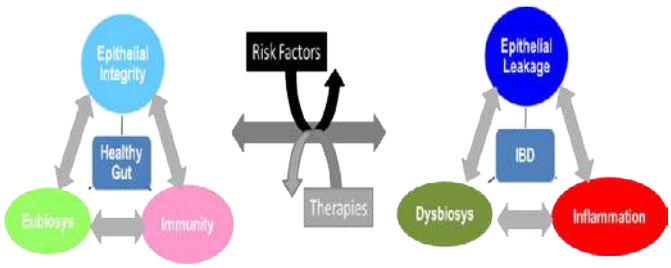


Image 1: Causal relationship between a healthy gut and IBD gut

Although the exact cause of the UC and CD is unknown, but epigenetic and environmental factors which affect the symbiotic ambience of gut microbiota and the overall immune status of the host body are the major causes thought to be the initiators of IBD. The disruption in the intestinal wall integrity, by virtue of breakage of the tight junction between intestinal epithelial cells, compromises the differentiation between good and bad bacteria on two sides of the intestinal wall. And this in turn provides an immunologically flared-up milieu of inflamed epithelial wall.

The human gut is the home for hundreds of trillion of bacteria and it is exposed to the constant flux of environmental bacteria that get ingested into our body through several pathways [7]. The pathogenic and commensal bacteria get distinguished by our innate immune system through the pattern recognition system. The pathogenic bacteria are eliminated by several mechanisms including the antimicrobial peptides secreted by intestinal epithelial cells in the gut epithelia. The commensal bacteria stays in symbiosis with the gut microbiota and protected from crossing the gut epithelia barrier by the integrity of epithelia cells through the protective mucous layer in the surface of the intestinal epithelial cells as well as by the tight junction protein which held epithelial cells tightly. The gut-associated lymphoid cells constantly sample the composition of the

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luminal environment and provide immunity to the gut barrier by pattern recognition and destroying pathogenic bacteria to maintain the integrity of the cellular lining [8]. But with the constant onslaught of different environmental factors on the intestinal epithelial cells by non-fibrous foods or dehydrations or low mucous production, the mucous barrier on the epithelial cells gets reduced, and for other reason the tight junction proteins also get lost. By these, the integrity of the intestinal epithelial lining gets compromised. This loss of strict seal of mucous barrier and tight cellular integrity creates a leaky gut wall, which in turn allows commensal bacteria to enter into the basal side of the intestine, lamina propia.

In a leaky-gut-environment, the innate immune system of the gut-associated lymphoid system sends out macrophages and dendritic cells to destroy those pathogenic bacteria and activates T cells to alert the immune system through inflammatory signals. The composition of the bacterial community changes during these instances. Although the interplay between leaky-gut, inflammation and dysbiosis of bacterial community is the real cause of the disruption or disease condition, but the true sequence of events or triggers are unknown. The gut-associated lymphoid system, consisting of innate immune cells, is activated and produces more inflammatory cytokines to keep the systemic immune balance. This balance goes out of hand with a constant influx of commensal bacteria in a leaky gut and slowly spreads all over part of the colon. A pan colitis kind of situation leads to the development of colon cancer [9].

The inflamed leaky gut lining is seen in the colonoscopies of both CD and UC patients. Intestinal epithelial cells show almost no mucous barrier and lost tight junction between cells. Major inflammatory cytokines like tumor necrosis factor alpha (TNFα), interleukin-8 (IL8), interleukin-6 (IL6), and interleukin-1-beta (IL1β) are seen in very high level in the circulating plasma of those patients [10].

a) Present treatment paradigm

The first-line therapy of IBD, at present, is mesala mine for a mild to the moderate condition of patients. Corticosteroids are used for severe conditions but with significantly high level of associated side effects. Immuno suppressants are also used for severe cases, but again with limitation as they have many a lot side effects. The biologics like Infliximab are not widely popular due to their high cost and low level of response rate [11, 12].To a physician, the main goal of the treatment of IBD patient is to contain the remission. Reducing the inflammation to stop further damages and flare up the disease. Mucosal repair of the intestinal epithelial cells is another critical point of clinical significance to cure the disease and bring back the gut wall to its native form which are majorly investigated by colonoscopies during the treatment regimen [13]. Integrin inhibitors like Vedolizumab and Etrolizumab are used to limiting the infiltration of immune cells into lamina propia side of the gut wall. JAK inhibitors, IL23 antibody and IL22 antibody were used to contain the inflammatory signalling pathways [14, 15]. Even the non-pathogenic good bacteria was used to limit the spread of inflammation and reverse the course of IBD in patients [16].

b) Gut-restricted function of present therapies

Several of the already approved IBD drugs exert their pharmacological action by modulating the components of factors present in the gut. The details of them are listed below in table 1.

Table 1: Approved gut-restricted drugs for the treatment of IBD

Drug	Route	Type	Mechanism of Action	Approved for
Mesalamine (Asakol & Lialda)	Oral	Small Molecule	Anti-inflammatory	CD/UC
Vedolizumab	IV	Monoclonal antibody	α4β7 integrin inhibition	CD/UC
Etrolizumab	IV	Monoclonal antibody	α4β7 integrin inhibition	CD/UC
Rifaximine	Oral	Small molecule	Anti-bacterial	CD/UC

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Mesalamine: The oldest among the drugs which act predominantly through the mechanism at the gut are Asacol and Lialda. They are the two different formulatory compositions of mesalamine. Both of them are prescribed as a first-line therapeutic option for mild to moderate UC and in a combination therapy for moderate to severe UC patients. Mesalamine, in its original form, is absorbed maximally in the small intestine leading to minimal exposure to the colon. The mechanism of action of mesalamine was through the modulation of multiple targets and was inconclusive as a major contributing pathway to the therapy. However few of the notables are, effect on mucosal cells, anti-inflammatory effects on immune cells, as an antioxidant including COX2 inhibition, modulating nuclear hormone receptors like PPARg, etc. The exposure proportional side effect to nephrosis, pancreatitis, and cardiac effect was a major concern, besides the immune-related side effects. But many clinical trials and their meta-analysis were inconclusive due to the heterogeneous complexity of the patient population, non adherence, and their symptomatic improvement without having a distinct molecular biomarker. During the 1980s, several clinical trials were run on different formulations of mesalamine to evaluate the efficacy of the drug from its distributive properties in the intestine [17]. Time-dependent enterocoated mesalamine (Pentasa) was released in the duodenum, and matrix metallo enterocoated formulations (Lialda and Mezavant) were released in the terminal ileum and entire colon. Prodrugs like Salfasalazine, Osalazine, and Balsalazine which were primarily released in the colon, were also evaluated with comparable efficacy but with side effects. pH-dependent mesalamine formulations (Asacol, Mesaal, etc) having a pH>6 were largely released in the colon and showed maximal efficacy. Colonic delivery of mesalamine was also evaluated in the trial [18]. Presently several delayed-release and enterocoated mesalamine formulations are available in the market, a few of them are Asacol HD, Delzicol, Apriso, etc. Considering the safety, efficacy, and adherence profile, presently gut-restricted or gut-released mesalamine is the most prescribed IBD medicine globally.

Antibodies which are acting on intestinal epithelial cells: Vedolizumab and Etrolizumab were two approved antibodies against α4β7 integrin for UC, which functions by blocking the interaction between α4β7 integrin and MADCAM-1 and thereby stopping the leukocyte adhesion to the endothelium. MADCAM-1 is mostly expressed in the gut-associated lymph nodes. Although given through the systemic route, these antibodies work at the site of inflamed intestinal epithelial where UC or CD exists [19].

Rifaximine: Rifaximine was approved in 2015 for the irritable bowel syndrome with diarrhea. It's an antibacterial agent that works through the inhibition of the transcription process by binding to bacterial DNA. It has no absorption into the systemic circulation after oral administration and devoid of many side effects. Clinical studies have shown significant promise of remission in CD (69%) and UC (76%). Detailed studies are required to establish it for therapeutic use [20].

c) *Upcoming gut restricted drugs for the treatment of IBD*

Table 2: Upcoming gut restricted drugs for the treatment of IBD

Drug	Company	Type	Mechanism of Action	Status
TD-1473	Theravance Biopharma	Small Molecule	Pan-JAK and TYK inhibition	Phase 2/3
PTG-100 PTG-943	Protagonist Therapeutics	Peptide	a4b7 integrin inhibition	Phase 2
JNJ67864 238 (PTG 200)	JnJ (Protagonist Therapeutics)	Monoclonal Antibody	IL23 inhibition	Phase 2
BT-11	Landos Pharma	Small Molecule	LANCL2 activation	Phase 2
BBT-401	Bridge Therapeutics	Peptide	Pellino-1 inhibition	Phase 2

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EB-8018	Enterome Biosciences	Small Molecule	FimH inhibition	Phase 1b
AVX-470	Avaxas Biologics	Polyclonal antibody	TNF inhibition	Phase 1
TD-5202	Theravance Biopharma	Small Molecule	Irreversible JAK3 inhibition	Phase 1
GB004 (AKB- 4924)	Gossamer Bio	Small Molecule	HIF1a stabilizer	Phase 1
Tenapanor	Ardelyx Inc	Small molecule	NHE3 inhibitor	Phase 3 Approved (IBS-C)
ST-0529	Sublimity Therapeutics	Small molecule	Cyclosporin nano formulation	Phase 2
Safalcone	Korean Univ	Small molecule	NRF2 inhibition	Discovery
unknown	Inflamazome	Small molecule	NLRP3 inhibition	Discovery

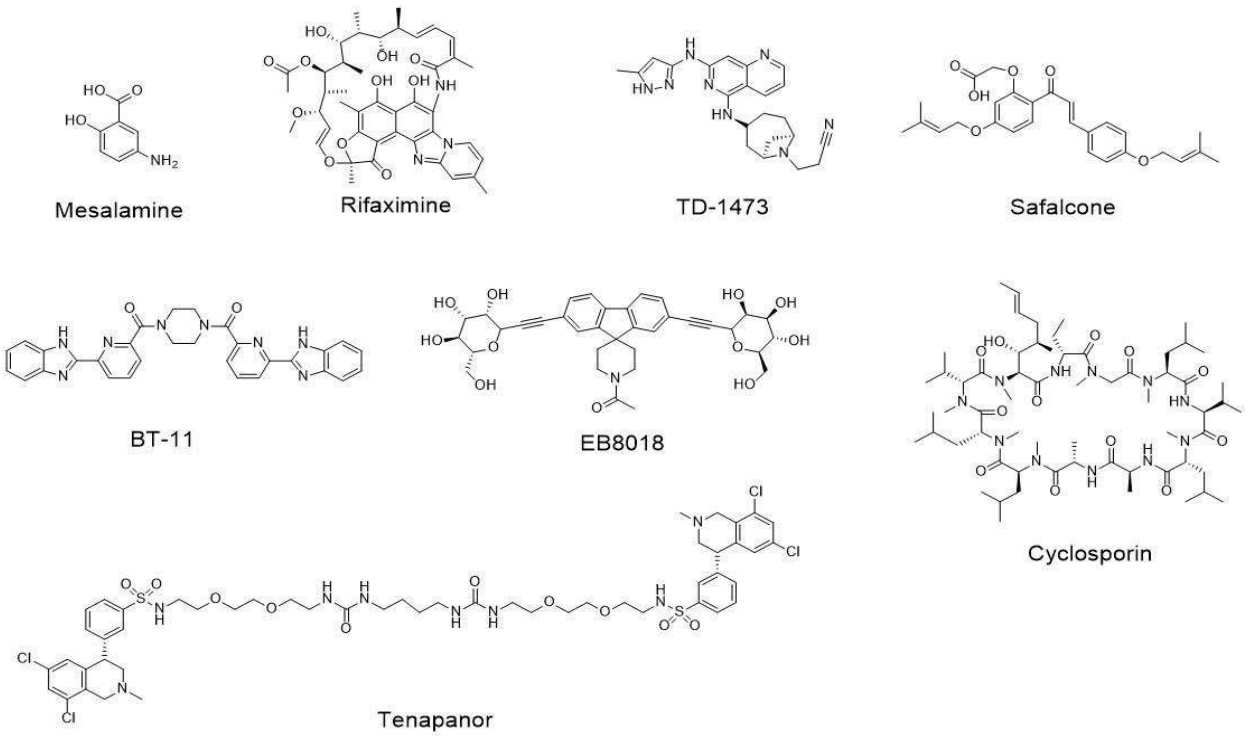


Image 2: Structure of known or disclosed small molecules drugs.

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i. *TD1473*

Theravance Biopharma initially tried to discover a unique formulation to make the pan JAK inhibitor tofacitinib to get restricted into the intestine and not to come into the systemic circulation to reduce the toxicity of systemic tofacitinib. Initial efficacy data in an oxazolone induced colitis model showed that the intracecal delivery of tofacitinib with 15 times lower dose had the similar efficacy and colon exposure even with 80 times lower plasma exposure to its oral delivery; providing the proof of concept about the local effect of JAK inhibitors in colonic gut epithelium Although initially, Theravance designed a gut restricted prodrug of tofacitinib, TD-3504; but discovered a chemically distinct new pan JAK, TYK inhibitor TD-1473 with gut restricted properties. In an oxazolone-induced colitis model, TD1473 showed a significant reduction of disease activity index at 1mpk oral dose, which is comparable to the 15mpk oral dose of tofacitinib in the same model. The oral exposures of those corresponding drugs were 4ng.hr/ml to 4.7ug.hr/ml which indicates that a gut-restricted compound with more than 1000 fold lesser plasma drug concentration can elicit the same efficacy, but only through the local gut effect. It also showed no immunosuppression, as generally observed with tofacitinib, by penetrating the intestinal wall to exert an anti- inflammatory effect locally on lamina propea and epithelial cells. It had slow absorption in the intestinal tract, but without any systemic plasma exposure [21].

Phase I clinical trial of TD-1473 with healthy volunteers for SAD (n=40) and MAD (n=32) showed tolerability upto 1000mg (SAD) and 300mg (MAD) for 14 days without any serious side effects. To extrapolate the similar observation from the preclinical pharmacokinetic pattern, in human also there was a low systemic exposure of the molecule and excreted largely through feces. A placebo-controlled exploratory phase Ib in 40 UC patients with 20 mg, 80 mg, and 270 mg doses showed >30% clinical response along with endoscopic mucosal healing (>20% patients) when treated for four weeks. Also, they had an improved histologic and rectal bleeding score. [22]. A significant percent of patients (>30%) showed the reduction of CRP and calprotectin without any immunosuppression (reduction of lymphocytes, leukocytes, and neutrophils) [23]. In collaboration with Jansen pharma, TD-1473 is now undergoing a phase 2 clinical trial in CD and phase 2b/3 UC patients [24].

ii. *PTG-100 and PTG-943*

The clinical proof of principal of α4β7 integrin inhibition for the treatment of UC and AD was established with the approval of monoclonal antibodies Natalizumab, Vedolizumab, and Etrolizumab. α4β7 integrin, majorly expressed in monocytes and macrophages, binds to the MAdCAM1 and VCAM1 in gut epithelial cells and Piears patches for T cell homing and thereby bacterial infiltration. Protagonist therapeutics discovered an oral small molecule cyclic peptide, PTG-100, as an α4β7 integrin antagonist whose exposure was restricted to gut. The molecule had a subnanomolar potency in inhibiting the α4β7 integrin and MAdCAM1 interaction while selective for VCAM and ICAM and in cellular adhesion assay as well [25]. This cyclic peptide showed great proteolytic and chemical stability in gastric fluid, intestinal fluid, plasma, and liver. PTG-100 showed almost no plasma concentration in rodents and mostly found in Peyer's Patches and colon (about 4uM). A similar effect was observed in a monkey PK study with an even higher colonic exposure of 15uM compared to any in plasma. [26]. PTG-110 showed efficacy in the rodent model on the prevention of T cell homing and mucus injury, most probably by a local effect on lymphoid cells of the intestine. In a placebo-controlled phase I clinical trial PTG-100 showed safety and tolerability till 100 mg dose with a high faecal concentration and extremely low plasma concentration [27]. The initial phase II data showed a dose-dependent target engagement saturating at about 60-70% level and receptor occupancy saturation at 300 mg dose. The histological remission was about 44% at 900mg dose. Further clinical testing was halted after an independent internal assessment of data predicted to be moderate efficacy of the molecule.

Instead, Protagonist placed a second-generation molecule PTG-493, which is superior to PTG-100 in every aspect in preclinical studies and early clinical studies. PTG-943 is about five times more potent and stays on target for about three times longer than PTG-100 in invitro assays. In monkey studies, it showed a higher level of target occupancy than PTG-100, although having similar low plasma exposure. In rat, it had about 400-500 times higher intestinal concentration than plasma. In healthy mice, PTG-943 was more effective in donor T-cell homing in illeal Lamina Propia as well as preserving colon integrity. In a phase I clinical studies, PTG-943 showed better target engagement of about 100% with a saturable receptor occupancy at 1000 mg dose [28]. A phase II clinical trial of PTG-943 is currently ongoing [29].

iii. *JNJ-67864238 (PTG200)*

JnJ-67864238 (PTG200) is an IL23 antibody developed by Protagonist Therapeutics in collaboration with Jansen Biotech. The recent FDA approval of Ustekinuzumab confirmed the proof of concept of the IL23 inhibition for the treatment of IBD. In addition to that, few more IL23 antibodies (Brazikumab, MEDI2070, BI655066, Mirikizumab, Guselkumab, and Risankizumab) are in advanced stages of clinical trials for their potential entry into the market. While all those antibodies were injectables, Protagonist Therapeutics with their special peptide technology discovered and developed a gut restricted antibody, PTG200, to inhibit

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IL23 locally in the intestine for IBD treatment. A TNBS induced rat colitis model showed dose-dependent improvement of the colitis parameters of body weight, colon length along with MPO, LCN2, and IL17 concentration in feces collected from distal colon and blood cytokines to validate the hypothesis of local IL23 inhibition with an oral gut restricted antibody [30, 31].

A randomised, double-blinded placebo-controlled phase I clinical trial of PTG200 demonstrated tolerability and safety of the molecule. Also, this study showed the consistent pharmacokinetics and pharmacodynamics of the gut-restricted properties. A phase IIb clinical trial is underway with 90 patients in Australia [32].

iv. *BT-11*

BT-11 is a first-in-class LANCL2 activator that is being developed by Landos Pharma [33]. CD4+ Treg cells control the production of inflammatory cytokines IFNγ, IL17, and TNFα to contain the flares of inflammation on the intestinal wall and gut mucosa. Lanthionine Synthetase Cyclase-like Receptor 2 (LANCL2) is majorly expressed in hematopoietic cells and gut-specific Treg and colon epithelial cells. Although, abscisic acid is the natural lig and for LANCL2, a computational approach by an academic lab produced a hit, which later optimized to give BT-11 [34]. BT-11 is a gut-restricted and locally acting (intestinal epithelium) molecule that is well tolerated until 1000mpk tested in rats and dogs. A 500mpk rat exploratory PK suggested a small but rapid absorption of the molecule with rapid clearance. The plasma concentration was very low, about 20 ng/ml at 500mpk dose [35]. A high volume of distribution (3.3L/kg) initially suggested a drug localization or non-systemic fractionation. BT-11 has been shown to be efficacious in various genetically and chemically induced rodent models of IBD, and along with the reduction of cytokines in the blood samples taken from CD patients, compared to the tofacitinib [36]. It showed the reduction of expression of TNFα in intestinal cells to promise a better or similar effect to a standard of care with TNFα inhibition with this new mechanism of action. A randomized, double-blind, placebo-control phase I SAD and MAD study of BT-11 with CD and UC patients (n=70) showed that 100mg of once-daily oral dose of BT-11 is safe. Drug concentration analysis showed a significantly low level (1:6000) of the drug in plasma compared to the feces and colon [37]. The faecal concentration increased dose proportionally. BT-11 showed a significant decrease of TNFα+, IFN+ CD4+ T cells, and an increase of FOXP3+ CD4+ T cells in colonic mononuclear cells from patients with CD and UC. A phase II clinical of BT-11 is undergoing [38].

BBT-401: BBT-401 is a potent first-in-class, gut restricted pellino-1 inhibitor discovered by researchers at Sungkyunkwan University and Korea Research Institute of Chemical Technology and later licensed and developed by Bridge Biotherapeutics. Pellino-1 is a ligase that plays a key role in multiple immune receptor signalling pathways, including Toll-like receptors, interleukin-1 receptor, and T-cell receptors [39]. BBT-401 is a lipidated tetra-peptide that binds to Pellin-1 and thereby dissociates the multiprotein signalling complex comprising of MYD88, RIP1, and others. In preclinical cellular and animal models, the compound showed the inhibition of TLR-NF B signalling and pro-inflammatory cytokine expression. In an animal model, it was shown to be safe in GLP tox studies. In animal models of colitis, compound showed significant efficacy with an improvement of colitis symptoms at a dose of 3mpk along with the mucosal healing. It was not systemically absorbed, and hence the efficacy was mainly attributed to the local effect of the molecule [40]. In a phase 1 clinical trial with 80 healthy volunteers, BBT-401 was found to be safe and well-tolerated till 1600 mg of daily doses for seven days. It was also shown that the molecule has no systemic exposure. A randomised, placebo-controlled, dose-dependent phase 2 study is undergoing right now [41].

v. *EB8018*

Enterome Biosciences developed a first-in-class non-biological, non-steroidal and non-anti-inflammatory small molecule drug for CD by inhibiting the FimH binding of the gut bacteria. Bacteria like AIEC (Adherent and invasive E. Coli) and Klebsiella bind to proteins like CEACAM6 that are overly expressed in chronically inflamed epithelial cells of the gut wall of CD and UC patients through the interaction of their FimH protein adhesion and thereby adhere to the gut cells and increases the bacterial concentration in gut mucosa [42]. FimH inhibition is also implicated in the urinary tract infection and other infections through the mechanism of biofilm formation [43]. Based on the available crystal structure of FimH and its natural ligand d-mannose, many efforts have been put to discover FimH inhibitors for therapeutics [44]. But most of the molecules suffered from metabolic and chemical instability in the GI tract. Disaccharides as well as monosaccharides with and without heterocycles were tried most. Many molecules showed unique physicochemical properties with high solubility but a very low systemic absorption, and stayed mostly in the intestinal tract. In a rodent model of CD, they showed a reduction of pathogenic AIEC in feces; and in the colonic and ileal mucosa showing early promise of the antiadhesive therapy [45]. Enterome developed EB8018 into phase I clinical trial and reported that the molecule is highly soluble and rapidly absorbed but only in a small amount (123ng/ml at 1500 mg dose) and mostly (97%) excreted through feces. The molecule was well-tolerated till 1500 mg dose with no clinically significant adverse effects that led to the

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progression of the molecule into phase II clinical trial. Takeda Pharmaceutical has collaborated on this [46].

vi. *AVX-470*

Avaxia Biologics [47] discovered AVX-470 (Avaximab), an oral gut restricted anti-TNF antibody for IBD. Although the systemic anti-TNF therapy for IBD was already approved (Adalizimab and Tofacitinib), but AVX-470 was designed to act only locally at the inflammation site of the gut wall of CD and UC patients to reduce the immunogenic and immunosuppressive toxicity associated with systemic anti-TNF drugs. AVX-470 was a lactose-free formulation of polyclonal immunoglobin (Ig) obtained from the early milk of cows immunized with recombinant human TNF and later enterically coated to pH 6.0. It was stable in GI track, resistant to the cleavage and digestion by peptidases. It was localized into the colon and had minimal systemic circulation. The molecule had a comparable in vitro potency to Infliximab. In a chemically induced (DSS or TNBS) mice colitis model, AVX-470 showed a significant reduction in disease activity score and inflammatory cytokines comparable to the standard of care like Prednisolone and a matched murine antibody (AVX-470m). Also, it was found to be penetrated into colonic mucosa to inhibit TNF driven mucosal inflammation [48].

A double-blind, placebo-controlled, phase I study (n=37) with three different doses of oral administration of AVX470 showed high intestinal localization of the drug and no traces in the blood circulation. The colonoscopic samples showed the presence in both luminal and basal side as it penetrated through the inflamed leaky gut epithelia. Twice daily dosing (till 3.5mg/day) showed no black box warning, which were generally present in systemic anti-TNF antibodies due to their immunosuppressive side effects In moderate to severe IBD patients, it showed similar efficacy in initiating the remission but better efficacy in maintaining the remission; comparable to systemic anti-TNF antibodies. It showed a significant reduction of CRP and IL6 [49].

vii. *TD-5202*

Recently Theravance has disclosed another gut selective irreversible JAK3 inhibitor (TD-5202) by taking advantage of the differentiated structural feature of an active site cysteine of JAK3. The exact structure and the preclinical data of this molecule are not available in the public domain. Again partnering with Jansen pharma, TD5202 is undergoing a phase I clinical trial indicating the inflammatory intestinal disease [50].

viii. *GB004 (AKB-4924)*

Aerpio Pharmaceuticals discovered AKB-4926, which later got licensed by Gossamer Bio to develop and commercialize for IBD as GB004. This is an oral gut restricted prolyl hydroxylase (PHD) inhibitor which selectively stabilizes Hypoxia-inducible factor 1-alpha (HIF1α). In a hypoxic condition, when oxygen demand from stressed cells are far more than the supply, master regulators like HIF1α gets over expressed to kick start induction of inflammatory genes to produce inflammatory cytokines and erythropoiesis [51]. In a disease condition like IBD, where gut epithelial cells suffer from stress and the high flux of inflammatory cytokines in a hypoxic condition, AKB-4924 plays a vital role in exerting an anti-inflammatory effect and mucosal healing effect by stabilizing HIF1α. They later proposed the detailed mechanistic pathway of HIF-IL-12p40 involvement in the Th1/Th17 pathway for HIF1α mediated mucosal healing [52]

Importantly, this molecule is gut-restricted when given orally and hence doesn't inhibit the systemic HIF1α which protects the renal and cardiac tissues, which are of general concern for this target to inhibit [53]. Also, AKB-4924 selective against HIF2α, which is otherwise known to cause inflammation. These were shown in a preclinical model of TNBS induced colitis in rats. Also, molecule showed the improvement of parameters of colitis and inflammation along with the mucosal healing of the protective effect of inflamed gut epithelial lining in this colitis model [54].

Gossamer Bio presently is running a placebo-controlled phase 1 clinical trial on GB004 to evaluate the safety, tolerability, and pharmacokinetics of the molecule on IBD patients [38].

ix. *Tenapanor*

Tenapanor is an inhibitor of sodium/hydrogen exchanger 3 (NHE3), located in the apical surface of the small intestine and colon and responsible for the intestinal absorption of dietary sodium. Ardelyx Inc [55] developed this compound for Irritable Bowel Syndrome with constipation (IBS-C) and got FDA approval in Nov 2019. By inhibiting the NHE3, Tenapanor decreases the sodium absorption and increases the moisture content of the mucosal surface. This effect results in the softening of the stool in patients. The molecule worked locally on the epithelial tissues of the colon and intestine [56].

In a phase I clinical trial, Tenapanor showed minimal absorption to the systemic circulation to below the detectable limit of 0.5ng/ml. The major excretion of about 70- 80% was through feces. In phase III clinical trial, it showed significant efficacy in patients with IBS-C [57].

x. *ST-0529*

Sublimility Therapeutics developed a proprietary SmPill technology, unlike IV or oral, for specific delivery of cyclosporine directly into the colon for moderate to severe UC patients. In a 100 patients phase 2a study, it showed good tolerability and safety to progress into 280 patient phase 2b study [58]. Earlier, it was reported that the cyclosporine (through IV route) had about 80% disease response in acute severe UC patients, who are refractory to steroid treatment, and that effect was similar to TNF therapy [59]. ST-0529 is now undergoing

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a clinical trial with the hope to provide safe and more efficacious cyclosporine for UC patients without major side effects.

xi. *Safalcone*

A recent publication from University of Korea showed that the anticolitic agent Safalcone when conjugated with natural amino acids to make it a gut-restricted compound, the inflammatory components, and the disease index were improved significantly in a TNBS rat model of ulcerative colitis. The molecule showed almost no systemic exposure and was excreted through feces. It was already known that the anti-colitis properties of Safalcone are achieved through the inhibition of NRF2 and HO-1 [60].

xii. *Inflazome*

Recently Inflazome disclosed their pipeline with a molecule in the pipeline in the discovery phase with a gut-restricted NLRP3 inhibitor for the treatment of UC and CD [61].

III. Conclusion

As the prevalence of the irritable bowel disease (IBD) cases is growing rapidly worldwide due to rapid industrialization, which causes major environmental changes and also the food habits of people especially those living in the urban setting changes, the need for a real disease-modifying therapy of IBD is of prime importance. Although presently, there exist numerous therapies, the response rate is not significant, and coupled with the low adherence to the therapy, creates a huge unmet need for patients suffering from this chronic disease. The remission of the disease is the most common factor in both UC and CD. Most of the present therapies come with a lot of side effects and comorbidities. When the disease gets severe, ultimately, almost ~30% of the patients go through the surgery for removal of the intestine after the 15-20 years of the diagnosis of the disease. Also, in very severe cases, IBD leads to colon cancer.

To avoid side effects arising out of systemic exposure to the drug and also to limit the mechanism of action localized to the site of the disease, there are number of efforts underway to make those drugs delivered in a gut-restricted manner so that the efficacy can be achieved maximally as well as the side effects arising out of systemic circulation of the drug can be contained. Considering the historical functioning of the existing drugs, mesalamine, and antibodies, pharma companies' effort on this unique mode of therapy could lead to a transformation to the therapy with more effective disease modification.

Conflict of interest: The authors declare that there is no conflict of interest. Both authors are employees of Cadila Healthcare Limited which fully owns Zydus Research Center.

Abbreviations

IBD	Irritable Bowel Syndrome
UC	Ulcerative Colitis
CD	Crohn's Disease
TNFα	Tumor Necrosis Factor alpha
IL8	Interleukin 8
IL6	Interleukin 6

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The Role of the Pharmacist in Patient Care (Book Review)

By Prof. B.K. Khanam

Dr. M. Nasirullah Memorial Trust

Abstract- Most people on the outside of the health care profession are unfamiliar with this new role of the pharmacist. The general public has portrayed a stereotypical pharmacist's picture as remain a person who stands behind a counter, dispenses medicine with some instructions to the respective consumer. Pharmacy practice has changed substantially in recent years. Today's pharmacists have unique training and expertise in the appropriate use of medications and provide a broad array of patient care services in many different practice settings. As doctors are engaged with the diagnosis and treatment of patients, the pharmacist can assist them by selecting the most appropriate drug for a patient.

Keywords: patient care; patient compliance; patient counseling; extemporaneous prescription compounding; framework for medication safety; patient behavior; patient education; patient-provider relationship; patient relationship management; patient problem solving and preventive care; pharmacovigilance; patient safety; pharmaco-economics; long-term care; community liaison pharmacists in home care; pharmacists in ambulatory care; critical care pharmacists; rational use of drugs; surgical dressing; medication risk management; medication history taking and reconciliation; drug related problems; medication reconciliation; palliative and hospice care.

GJMR-B Classification: NLMC Code: QV 4

THEROLEPHARMACISTPATIENTCAREBOOKREVIEW

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The Role of the Pharmacist in Patient Care (Book Review)

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Abstract- Most people on the outside of the health care profession are unfamiliar with this new role of the pharmacist. The general public has portrayed a stereotypical pharmacist's picture as remain a person who stands behind a counter, dispenses medicine with some instructions to the respective consumer. Pharmacy practice has changed substantially in recent years. Today's pharmacists have unique training and expertise in the appropriate use of medications and provide a broad array of patient care services in many different practice settings. As doctors are engaged with the diagnosis and treatment of patients, the pharmacist can assist them by selecting the most appropriate drug for a patient. Divine interventions by the pharmacists have always been considered as a valuable input by the health care community in the patient care process by radically reducing the medication errors, rationalizing the therapy and reducing the cost of therapy. The development and approval of the Pharmacists' Patient Care Process by the Joint Commission of Pharmacy Practitioners and incorporation of the Process into the 2016 Accreditation Council for Pharmacy Education Standards have the potential to lead to important changes in the practice of pharmacy, and to the enhanced acknowledgment, acceptance, and reimbursement for pharmacy and pharmacist services. As an author, it is my heartiest believe that the book will adjoin significant apprehension to future pharmacists' in-patient care as most of the portion created from recently published articles focusing pharmacists in patient care settings.

Keywords: patient care; patient compliance; patient counseling; extemporaneous prescription compounding; framework for medication safety; patient behavior; patient education; patient-provider relationship; patient relationship management; patient problem solving and preventive care; pharmacovigilance; patient safety; pharmaco-economics; long-term care; community liaison pharmacists in home care; pharmacists in ambulatory care; critical care pharmacists; rational use of drugs; surgical dressing; medication risk management; medication history taking and reconciliation; drug related problems; medication reconciliation; palliative and hospice care.

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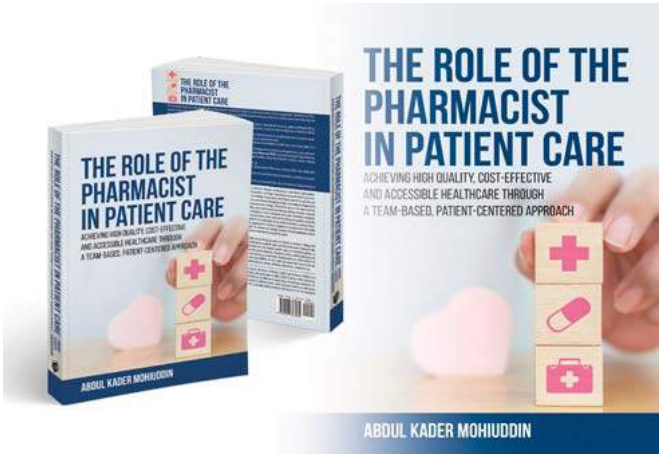


Figure 1: Book Cover Page. [Publisher: Universal-Publishers (US). (ISBN-10: 1627343083, ISBN-13: 9781627343084)]



Figure 2: The Author

I. Introduction

The goal of excellent quality, cost-effective and accessible health care for patients is achieved through team-based patient-centered care. Pharmacists are essential members of the healthcare team. The profession of pharmacy is continuing its evolution from a principal focus on medication product distribution to expand clinically oriented patient care services. As an unfortunate result of this professional evolution, the paramount importance of, and need for a consistent process of attention in the delivery of patient care services has been increasingly recognized by the

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profession at large. Pharmacists in hospital, community care, dispensing and allied healthcare arena are highly appreciated for their knowledge-based contribution and dedication towards the profession. The practical purpose of the published book efficiently is to properly guide the patient care pharmacists in their modern day to day activities. Along with specific guidelines, the book encloses ideas about patient dealing, patient rights, ethical decision making, professionalism. At every chapter, the role of pharmacists in that chapter specific issues are detailed explicitly so that a professional pharmacist or a student can figure out she or his do and not to do in that specific situations. Moreover, further reading references are typically listed to naturally follow specific guidelines further. Therefore, the book is an archive of potential references too. Among so many books on clinical pharmacy, hospital and community care pharmacy the role of pharmacist's in-patient care is rarely highlighted with a very little information. The key sector is emerging in both developed and under-developed countries. In most of the books, either doctor or nurses' roles are highlighted. The proposed book (*Figure 1*) highlights pharmacists' roles and responsibilities to the most, separated from those of doctors and nurses, with most recent information obtained from recently published articles of several journals, books, newsletters, magazines etc. The book's chapter-based summary is added in *Table 1* and comparison with similar other available books given in *Table 2*.

II. Pharmacist's Role in Patient Care

The development and approval of the Pharmacists' Patient Care Process by the Joint Commission of Pharmacy Practitioners and incorporation of the Process into the 2016 Accreditation Council for Pharmacy Education Standards have the potential to lead to important changes in the practice of pharmacy, and to the enhanced acknowledgment, acceptance, and reimbursement for pharmacy and pharmacist services [1]. Nowadays, pharmacists also ensure the rational and cost-effective use of medicines, promote healthy living and improve clinical outcomes by actively engaging in direct patient care and collaborating with many healthcare disciplines. With this expanding scope of modern practice, practicing pharmacists are being recognized as key components in traditionally providing individualized patient care as key part of interprofessional healthcare teams [2]. Pharmacists help manage complex patients because they look at medications with a distinctive eye than a doctor. One essential practice they efficiently perform in common is a "comprehensive medication review" where likely patients bring in medications, vitamins, necessary supplements, and OTC drugs [3]. Nowadays, the possible shortage of health personnel, and in particular pharmacists, remain a challenging issue that the health systems inevitably have to face. The practical use of a current technology like tele pharmacy can represent a possible option to combat these problems [4]. Up to 50% of ADE and ADE-related hospitalizations are judged to be preventable by avoiding inappropriately prescribing. Use of a simple interdisciplinary medication review has been shown to naturally lead to the reduction of inappropriate prescribing and costs, but there was no effect on clinically relevant patient outcomes, possibly due to a lack of power and insufficient observation time [5]. Pharmacists accompany their patients somewhere between 1.5 and 10 times more frequently than they see primary care physicians [6]. Clinical pharmacists can support patients, manage their medicines and reduce their anxiety about receiving multiple medicines [7]. Practicing pharmacists also gets benefit because there are an increased recognition and mutual respect for the social value of the practical advice and active service that they amply provide [8]. There is a need to increase access to primary care services, control costs, and improve outcomes in health care for patients especially in the management of chronic conditions which puts a strain on health care systems worldwide [9]. Pharmacists' better access to the likely patients and their acceptability radically improve patient care by enabling pharmacists to fulfill an even greater role in the provision of safe and effective unscheduled care, treating common clinical conditions and responding to emergency requests for medicines [10]. Therefore, students who are interested in patient care practice as their future career, should develop a standardized approach to assessing, prioritizing, and resolving drug-related problems such as untreated conditions, appropriate drug selection, duplication of therapy, use of drugs without a condition or indication, over or under-dosing, adverse effects or toxicity, allergic reactions, drug interactions, adherence, availability and access, cost, and outcomes expectations. Prospective students also should be looking for the beneficial outcomes of drug therapy and pharmacy services with mutual respect to patient understanding, disease and disorder prevention, and medication-associated efficacy and safety.

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Table 1: Book Compendium

Chapter	Synopsis
Chapter 1.	**Pharmacy Practice at a Glance** Pharmacy in common is the art and science of carefully preparing and dispensing medications and the key provision of drug-related information to the consuming public. It typically involves the modern interpretation of prescription orders; the compounding, labeling and dispensing of drugs and devices; drug product selection and drug utilization reviews; patient monitoring and appropriate intervention; and the provision of cognitive services related to proper use of medications and modern devices. The current philosophy or approach to competent practice in pharmacy is designated as pharmaceutical care. This concept holds the important role of the pharmacist is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. Pharmacists, then, are those who are educated and licensed to dispense drugs and to provide drug information—they are typically leading experts on used medications. They remain the most accessible member of today's health care team, and often are the first credible source of assistance and advice on many common ailments and health care matters.
Chapter 2.	**Pharmacists in Clinical Pharmacy Practice** Clinical pharmacy gently took over a key aspect of medical care that had been partially abandoned by practicing physicians. Overburdened by patient loads and the terrific explosion of modern drugs, practicing physicians turned to pharmacists more and more for drug information, especially within institutional settings. Clinical pharmacy is genuinely concerned with both medicines policy and the effective treatment of ill patients, with the ultimate aim of achieving optimal use of medicines. Hospital clinical pharmacists typically interact with patients on wards, on multi-profession ward rounds or in clinic settings to treat, monitor and allegedly advise on the possible use of medicines. However, CP clearly includes more than just direct patient care. Therefore, activities like production of guidelines and policies, advising on drug expenditure controls, training and education of other healthcare professionals are also included.
Chapter 3.	**Pharmacists in Hospital Management** The modern advancements in preventive medicine and innovative technology have graciously allowed care that once required the intensive care of a hospital setting to be delivered in less intensive settings. As a result, we have witnessed the historical development of ambulatory surgery centers, skilled nursing facilities, home health services, outpatient treatment centers, and multiple chronic disease monitoring programs. Health care leaders continually search for the delivery model that approaches the quality, safety, and access expectations of patients at an affordable cost. This quest led to a progression from particular stand-alone hospitals to health systems. These "comprehensive health systems" inevitably include the acute care services that only hospitals are equipped to provide and a cadre of other services that may include primary care, specialty outpatient care, home care, nursing home facilities, hospice care, ambulatory surgery programs and a network of physicians and other healthcare providers.
Chapter 4.	**Pharmacists in Community Care** Community pharmacy comprises all of those establishments privately owned and whose function, in varying degrees, is to serve society's need for both drug products and pharmaceutical services. It is challenging to characterize or describe the typical pharmacy because of the considerable variance among them. They typically range from the corporately owned chain pharmacy, to the pharmacy department in a supermarket, to the independently owned pharmaceutical center that provides prescription service plus a relatively few lines of health-related products. Although heterogeneous in some respects, as in type of ownership and type of goods and services offered, community pharmacies generally are recognized by the public as the most accessible source of drugs and information about drugs.
Chapter 5.	**Patient Rights and Ethical Care** Patients also have a right to treatment that is both safe and effective within given parameters.The fundamental question that must be posed prior to considering any medical or surgical treatment for a patient is, Is the treatment realistic and effective? Such a proper standard for drugs has been in effect since the passage of federal legislation in the initial part of the 20th century. Not only must a drug be shown to be effective—that is, able to produce the effect for which it was administered— it must work with a certain degree of safety. Patients typically choose their own physician, pharmacy, and hospital. Likely patients are knowingly allowed to choose from multiple options of effective treatment when they traditionally exist. Patients must confirm their approval, through the process of informed consent, prior to the initiation of care. All of the preceding presupposes that treatment is available and that the patient possesses the economic wherewithal to pay for that treatment. For uninsured patients or lack the ability to pay, the fundamental right to voluntarily choose the divine nature of their affordable health care is meaningless.
Chapter 6.	**Prescription** The prescription order is a part of the professional relationship among the prescriber, the pharmacist

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and the patient. It correctly is the practicing pharmacist's grave responsibility in this relationship to properly provide quality pharmaceutical care that adequately meets the medication needs of the patient. The pharmacist must be precise in the manual aspects of typically filling the prescription order and must provide the patient with the necessary information and guidance to solemnly assure the patient's compliance in taking the medication properly. It is also the pharmacist's ultimate responsibility to advise the prescriber of drug sensitivities the ill patient may have, previous adverse drug reactions (ADRs), and,or other medications that the patient may be taking that may alter the effectiveness or safety of the newly or previously prescribed medications. Practicing pharmacists now find themselves frequently contacting physicians to respectfully suggest alternative drug products for individual patients as dictated by the formularies used by third-part prescription insurance plans. To meet these responsibilities, it is essential the pharmacist maintains a high level of practice competence, keeps appropriate records on the health status and medication history of his or her patients and develops professional working relationships with other health professionals.

Chapter 7. Prescribing

While drugs possess the capacity to enhance health, they all offer the potential to cause harm if prescribed inappropriately. For this reason, it is recommended that healthcare professionals who prescribe medications exercise critical reasoning skills to ensure the cautious and effective use of therapeutic agents. Pharmacists undoubtedly have crucial role plays in both handling prescription and prescribing. A rational prescribing is the sole of patient safety, patient compliance and patient relief. This published paper proposes aims that a prescriber should try to achieve, both on first prescribing a drug to maximize effectiveness, minimize risks and costs, and respect the patient's undeniable need.

Chapter 8. Patient Counseling

The patient has an altered mental state mostly driven by emotional disturbance for being ill. Along with that cultural and economic factors gives rise to a fundamental question of out of the pocket expense. Any private counseling or consultation provided should be traditionally done in a gentle manner which universally respects the patient's privacy and maintains confidentiality. Nothing should be taken for granted regarding the patient's personal understanding of how to use medication and appropriate steps must be taken to provide likely patients with the information and counseling necessary to manage their medications as effectively and as safely as possible.

Chapter 9. Extemporaneous Prescription Compounding

Pharmacy activities to individualize patient therapy traditionally include compounding and clinical functions. Either function in the absence of the other results in placing pharmacy in a disadvantaged position. It is significant to use a pharmacist's personal expertise to carefully adjust dosage quantities, desired frequencies, and even dosage forms for enhanced compliance. All pharmacists should properly understand the viable options presented by compounding. Pharmaceutical compounding is increasing for a number of possible reasons, including the availability of a limited number of dosage forms for most drugs, a limited number of strengths of most drugs, home health care, hospice, the non-availability of drug products,unusual combinations, discontinued drugs, drug shortages, orphan drugs, alternative therapeutic approaches and special patient populations (pediatrics, geriatrics, bioidentical hormone replacement therapy for postmenopausal women, pain management, dental patients, environmentally and cosmetic sensitive patients, sports injuries and veterinary compounding).

Chapter 10. Framework for Medication Safety

Appropriate medication use is a complex process involving multiple organizations and professions from various necessary disciplines combined with a practical knowledge of medications, access to accurate and complete patient information and integration of interrelated decisions over a period of time. The increasing complexity of modern science and technology naturally requires health care providers to know more, manage more, monitor more, and involve more care providers than ever before. Current methods of organizing and delivering care are not able to meet the new expectations of patients and families because the knowledge, skills, care options, devices, and medications have advanced more rapidly than the health care system's ability to deliver safety to them, effectively, and efficiently. The potential for errors of notable omission or commission to creep into the gradual process is extraordinary. No one clinician can retain all the information necessary for overseeing sound, effective, most recommended practice. This is substantially accurate in the case of pharmaceutical delivery and development.

Chapter 11. The Enigma of Patient Behavior

Patients today are considered to be typically thinking, able decision makers who can play an important role in the treatment process. Because patients are now recognized as active individuals, more focused attention is being paid to ways of restoring ill health or slowing illness progression through improved provider-patient communication and patients' involvement in their own treatment. Emphasis, therefore, is placed on a range of patient treatment behaviors including sharing beliefs and expectations, asking questions, adhering to regimens, using home monitoring devices, keeping appointments, identifying and reporting side effects and drug-taking problems, and other valuable forms of necessary communication in contemporary health care.

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Chapter 12. Patient Education

Patient education ensures healthcare team is working together on patients' individual medication plan, in conjunction with the rest of treatment, is vital to your recovery. Medication management is part of every patient's plan of proper care. On an initial visit a clinician completes comprehensive medication reconciliation. However, education is provided to every patient based on each medication the patient is prescribed. This includes its purpose, how and when to take it and how much of the medication to take. Education may be provided by any healthcare professional that has undertaken appropriate training education, education on patient communication and education is usually included in the healthcare professional's training. Health education is also an effective tool used by managed care plans, and may include both general preventive education or health promotion and disease or condition specific education. Important elements of patient education correctly are skill building and ultimate responsibility: patients need to know when, how, and why they need to make a lifestyle change. Group effort is equally important: each member of the patient's health care team needs to be professionally involved.

Chapter 13. Patient-Provider Relationship

The Provider-Patient Relationship is a recent idea of medicinal human science in which patients intentionally approach a specialist and, in this way, turn into a piece of an agreement in which they will in general reside with the specialist's direction. It has been recommended that a perfect relationship has specifically deliberate decision, professional's enhanced capability, great correspondence, genuine compassion by the considered specialists, congruity, and no irreconcilable circumstance. Truth be told, a poor relationship has been turned out to be a noteworthy impediment for the two specialists and patients and has in the end influenced the nature of medicinal services and capacity of the patients to adapt to their disease. Inferable from the poor relationship, patients do not demonstrate consistence with specialist guidance totally; pick the expert - by changing their professional over and over; stay on edge; may pick quacks or other non-logical types of preferential treatment; critical increment in immediate and roundabout restorative costs. In view of intermittent change in line of treatment according to the counsel of various experts and non-culmination of the whole course of medications, there is an unmistakable extension for the rise of antimicrobial opposition, which further intensifies the medicinal expense and tension, lastly may create genuine types of malady or complexities. From the experienced professionals' point of view, they may respectfully request superfluous examinations or may give over-medicines, as a sanity check. There is likewise watched an amazing decrease in human touch or sympathy; and a noteworthy ascent in unfortunate rivalry among specialists.

Chapter 14. Patient Compliance

With affectionate regard to the used provision of health care, the concept of compliance can be viewed broadly, as it relates to instructions concerning diet, exercise, rest, return appointments, etc., in addition to the use of drugs. However, it is in lively discussions concerning drug therapy that the designation patient compliance is employed most frequently. It is in this context that it will be utilized in this discussion, and compliance can be defined as the extent to which an individual's behavior coincides with medical or health instructions,advice. Patient compliance with therapy implies an understanding of how the medication is to be used, as well as a positive behavior in which the patient is inspired sufficiently to use the prescribed treatment in the manner intended, because of a perceived self-benefit and a positive outcome (e.g., enhanced daily functioning and well-being).

Chapter 15. Patient Relationship Management

In the healthcare sector the key customers are patients. Hospitals may offer better care by establishing a long-term relationship between the hospital and a patient. The primary reason for investing in building beneficial relationships with patients is a limited number of patients in the therapeutic segment or of long-term care and only clinics aware of this fact that can attach to each patient have a chance to build a sustainable advantage. Encouragement of the patient to continue to utilize the services of a company,provider is a procedure several times more reasonable than convincing current patients. Developed or under developed country, patients maintain a similar need for understanding and following treatment guidelines which is truly impractical for long term care without personal supervision. So many factors are behind patient relationship but one thing clearly understood that the handling of such situations is a provider's function, a regular follow up through taking different measures along with treatment intervention.

Chapter 16. Patient Problem Solving and Preventive Care

Pharmaceutical care remains a straightforward concept. It intimately involves the pharmacist working in concert with his patients and other healthcare providers to identify, monitor, and achieve desirable health-related outcomes through the appropriate use of medications. The care provided must be scientifically based upon a logical, effective, and patient-specific pharmaceutical care plan. There is an ancient saying, "an ounce of prevention is worth a pound of cure." This has never been true in health care. Routine follow-up with primary care physicians and other health care professionals can aid in the initial detection of many medical conditions (e.g., discovered cancer, diabetes, essential hypertension)

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and can gently encourage healthy habits that prevent the development of other conditions (e.g., Hormone replacement therapy, substance abuse, obesity prevention, thyroid disorders, etc.).

Chapter 17 **Pharmacovigilance**

Pharmacovigilance fundamentally comprises safety of prescription. It is the science and movement associated with collection, detection, assessment, monitoring, and counteractive action of untoward impacts with pharmaceutical items. Drug specialists have entered the job in wellbeing frameworks to keep up the objective and safe utilization of medication for they are sedate specialists who are unequivocally prepared in this field. The perspective of drug store understudies on pharmacovigilance and ADR announcing has additionally been talked about with a mean to center the need to improve content identified with ADR revealing and pharmacovigilance in undergrad drug store academic programs. Globally, despite the fact that the job of drug specialists inside national pharmacovigilance frameworks varies, it is exceptionally all around perceived. Reconciliation of ADR detailing ideas in instruction informative programs, preparing of drug specialists and willful commitment of drug specialists in ADR announcing is essential in accomplishing the safety objectives and preservation of general wellbeing. Additionally, these learning holes can be placated through ceaseless expert improvement projects and reinforcing hypothetical and viable information in undergrad drug store informative programs. Without adequately recognizing and acknowledging preparing requirements of drug specialists and other social insurance experts, the ability of national pharmacovigilance frameworks is likely not going to enhance which may trade off patient's safety.

Chapter 18 **Patient Safety**

Patient safety is a global concern and is the most noteworthy areas of medicinal services quality. Medical error is a noteworthy patient safety concern, causing increment in medicinal services cost because of premature mortality, morbidity, or broadened clinic remain. A definition for patient safety has emerged from the medicinal and similarly unique services quality development, with different ways to deal with the more solid basic segments. Patient safety was characterized as "the counteractive action of damage to patients." Importance is put on the arrangement of consideration conveyance that blocks errors; gains from the errors that do happen; and is based on a culture of safety that includes medicinal services experts, associations and patients. Patient safety culture is a multifaceted marvel. Patient safety culture appraisals, required by universal accreditation associations, enable services associations to acquire an unmistakable perspective of the patient safety viewpoints requiring critical consideration, recognize the qualities and shortcomings of their safety culture, help care giving units distinguish their current patient safety hitches, and benchmark their scores with different healthcare settings.

Chapter 19 **Pharmaco-Economics**

Cost-benefit analysis and other pharmacoeconomic tools are ways to analyze the value of the service to the public. These methods supplement the traditional marketplace value as measured by the prices that the patient or patron is willing to pay. As third parties continue to pay for a higher percentage of prescriptions dispensed, pharmacy managers are very cognizant that pharmacy services require continual cost-justification to survive and thrive in the future. The continuing impact of cost-containment is causing administrators and key policymakers in all health fields to examine closely the costs and benefits of both proposed and existing programs. It is increasingly evident private employers and public agencies are demanding that health programs be carefully evaluated in terms of clinical and social outcomes related to costs incurred.

Chapter 20 **Long Term Care**

Pharmacist involvement in long-term care activities grew as a result of these regulations, which include oversight of key provision of medications to nursing facilities and consultant pharmacist duties. Pharmacists traditionally practicing in the field of geriatrics must not only be cognizant of these guidelines, but must also be capable to manage ill patients with multiple disease states taking multiple medications. Policies and standard procedures for organizational aspects, medication orders, ordering and receiving medications from the pharmacy, medication storage in the nursing facility, disposal of unused medications, medication administration, and medication monitoring are required in long-term care facilities.

Chapter 21. **Community Liaison Pharmacists in Home Care**

The provision of home care has existed since the turn of the last century, when societal concerns regarding immigration, industrialization and infectious diseases spawned the need for visiting nurses. Early homecare services primarily consisted of midwife and nursing assistance for births, and the proper care of influenza and tuberculosis patients. This prior form of home care paved the way for the development of alternate site healthcare. In the historic past, the term home care generally referred to community-based nursing services provided to likely patients in their private homes. This day, the term has been expanded to include home,alternate site healthcare and encompasses: long-term care and skilled nursing facilities, assisted living and subacute facilities, home care, diagnostic centers, outpatient clinics, ambulatory surgery, rehabilitation facilities, and emergency service markets.

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Chapter 22. Pharmacists in Ambulatory Care

Pharmacy is evolving from a product-oriented to a patient-oriented profession. This role modification is extremely healthy for the patient, the pharmacist, and other prominent members of the health-care team. However, the evolution will present pharmacists with a number of new challenges. Now, more than in the past, pharmacists must make the acquisition of contemporary practice knowledge and skills a high priority, to render the level of service embodied in the concept of pharmaceutical care. Pharmacy educators' organizations and regulatory bodies must all work together to support pharmacists as they assume expanded health-care roles. Pharmacy and the health-care industry must work to ensure the pharmacist is compensated justly for all services. But before this can happen it will be necessary for pharmacy to amply demonstrate value-added to the cost of the prescription. Marketing of the practical purpose of pharmacy in the health-care morass and of the services provided by the pharmacist is needed to generate an appropriate perceived value among purchasers and users of health-care services. Practicing pharmacists should view themselves as dispensers of effective therapy and drug effect interpretations as well as of potential drugs themselves. Service components of pharmacy should be identified clearly to third-party payers and be visible to consumers, so that they know what is available at what cost and how it may be accessed. In the future, pharmacy services must be evaluated on the patient outcome (i.e., pharmaceutical care) rather than the number of prescriptions dispensed, and pharmacy must evolve toward interpretation and patient consultation, related to the use of medication technologies.

Chapter 23. Pharmacists in ICU

Clinical pharmacists deliver an essential contribution to the cautious and effective use of medicines in critically ill patients. Few niches clinical pharmacy areas have documented the powerful impact a pharmacist's presence can have in the way it has been done in critical care. Direct patient care via pharmacist medication review remain a significant resource for reducing medication errors and optimizing medication use. Specific recommendations for changes to medication therapy related to these medication reviews have very high acceptance rates by critical care medical teams. The pharmacist prescribing to action the outcomes of their own medication reviews would be anticipated to reduce the workload of medical colleagues and improve efficiency. Moreover, pharmacist instigation of medication therapy planned by the multidisciplinary team may also offer advantages with respect to getting treatment right the first time in specific areas, for notable example, therapeutic drug monitoring or drug dosing in multiorgan failure.

Chapter 24. Rational Use of Drugs

Many medicines now exist on that, can prevent, alleviate, treat, or cure diseases which previously took inordinate tolls on the health and well-being of children, families, communities, and populations. However, the overuse, underuse, or misuse of medicines (also referred to as irrational medicine use) presents these advances in jeopardy and, in addition to squandering limited resources, threatens future public health gains. The challenge of irrational medicine use endures a global one—common to all countries and all healthcare settings. Both healthcare providers and patients contribute to irrational medicine use. Leading providers may prescribe too many, too few, or inappropriate medicines; or may prescribe the appropriate medicines in the wrong dose, formulation, or duration. Additionally, patients voluntarily contribute to irrational medicine use through self-medication, pill sharing, or not completing a treatment regimen as prescribed.

Chapter 25. Surgical Wound Enrichments

Wound healing remainsan extremely complex process that results in the restoration of cell structures and tissue layers after an injury. It involves interdependent and overlapping cellular, physiological, biochemical, and molecular processes. There are numerous wound dressings and management techniques available today. The challenge lies not only in choosing the correct dressing, but also in demonstrating the chosen technique properly. This involves thorough assessment of the wound, taking into account its size, the exudate, and the patient's preferences. Health care professionals require essential knowledge of dressings for appropriate application, and the wound should be monitored carefully to ensure effective healing. Pharmacists can encourage improvement in wound care for patients who have recently undergone surgery by aiding them select the appropriate postsurgical wound care products and by educating them on proper wound care.

Chapter 26. Medication Risk Management

Medications are the most common treatment intervention used in healthcare around the world. Medication is administered to almost every patient in hospital and can endure the most leading part of treatment. When used safely and appropriately, they contribute to significant improvements in the health and well-being of patients. However, medication is not without risk and occasionally medications can cause harm. Medication safety issues can impact health outcomes, length of stay in a healthcare facility, readmission rates, and overall costs to the healthcare system. Some harm caused by medicines is due to preventable errors. The US FDA approve drugs only if they are determined to be safe to use for the conditions described in their label. This fundamental tenet of the Food, Drug and Cosmetic Act has not changed. What has changed however in recent years represent the interpretation of the term

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"safe."Modern concepts of pharmaceutical risk management are based on the premise that drug manufacturers, health care professionals, and patients have a responsibility to minimize the risks of using pharmaceutical products. Hospitals and health services aim to prevent harm by: perceiving what contributes to these errors, taking action, sharing this information with the community and health professionals. It is not enough to make drugs minimally safe; they must be as safe as possible over the lifecycle of the product's use. However, starting in the early 1990s, FDA began to carry out a more active role in post-marketing surveillance and began instituting a more aggressive "management" process to assure greater safety in the practical use of marketed drugs. No longer do the manufacturer and FDA provide passive oversight and labeling changes to control risks, now the manufacturer must actively monitor for suspected but unquantified risks and actively manage and minimize known risks.

Chapter 27. Medication History Taking and Reconciliation

Patients are at risk of DRPs at transition points during necessary hospitalization. The community pharmacist is frequently the first healthcare professional patients visit after discharge. Medication reconciliation, the process of identifying the most accurate list of all patient's medications represent a strategy to identify many medication discrepancies and reduce potential harm. Medication reconciliation at transitions of care decreases medication errors, hospitalizations, and adverse drug events. Obtaining medication histories and conducting medication reconciliation are challenging tasks for the health professionals. Part of ADEs is due to medication discrepancies, or unexplained variations in medications in hospital admission and discharge or across various sites of care. Significant number of all hospitals prescribing errors typically originate from incorrect admission medication histories, the DRPs are only discovered through patient interview, and more than half of discharge discrepancies are associated with admission discrepancies. ADEs positively associated with medication discrepancies can prolong hospital stays and, in the post-discharge period, may inevitably lead to emergency room visits, hospital readmissions, and utilization of other healthcare resources Pharmacists have proven themselves in both histories recording and reconciliation. True collaboration with allied health professions enhances this process. A reconciliation of medications supported by efficient communication between the hospital staff and community pharmacists, in notable addition to a standard patient interview and a general practitioner's examination of prescriptions, was found to be effective in identifying medication discrepancies for patients.

Chapter 28. Palliative and Hospice Care

One of the primary goals of medicine is to provide comfort and relief from pain and suffering. Unluckily, a cure is not always possible particularly in this era of chronic diseases, and the role of physicians has become limited to controlling and palliating symptoms. Palliative care efficiently is a relatively new specialty that evolved during the last five decades. The aim of this specialty was to provide the end of life care for patients with advanced cancer and their families. In addition, pastoral care is additionally included according to the religious beliefs of the patient. The other core components of palliative care are effective communication and planning and coordination of care. It is noteworthy that ensuring the availability of palliative care services represents an obligation of health care systems under international human rights law. Hospice care remains a type of palliative care with a few differences. Pharmacists in care team can carry out a leading role in different care settings.

Chapter 29. Non-Drug Pain Management

Prescription painkillers are compelling much of the time. Be that as it may, the relief from profound discomfort they offer includes some major disadvantages for some. Painkillers risk getting to be addictive. What's more, as endless news reports have appeared, the possible consequences of dependence on painkillers can be wrecking. Non-drug therapies reduce pain and can be utilized notwithstanding pharmaceuticals or in lieu of pharmaceuticals. They offer the likelihood to positively enhance personal satisfaction. Similarly, as with some other treatment, every individual will react distinctively to various therapies, and there is no proper certification that any treatment will give total help with discomfort. Though many evidences were weaker, the researchers also found that massage therapy, spinal manipulation, and osteopathic manipulation may provide some help for back pain, fibromyalgia, osteoarthritis, cancer pain, knee replacement, a migraine, frozen shoulder and chronic non-migraine headache. These data can equip providers and likely patients with the valuable information they need to have informed conversations regarding non-drug approaches for effective treatment of specific pain conditions. It's significant that continued research carefully explores how these holistic approaches in fact work and whether these consistent findings apply broadly in diverse clinical settings and patient populations.

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Key Features of the book

- → The book solely focuses on job responsibilities of patient care pharmacists, separated from those of learned doctors and qualified nurses, with the most recent information.
- → key various aspects of pharmacist-led patient care services are adequately incorporated in a particular book.
- → Career-focused discussions in every devoted chapter with structured guidelines provided for the practicing pharmacists.
- → Content is mostly based on recent pharmacists' activities in the healthcare arena of developed countries.
- → Chapter outline, standard abbreviations, synopsis, learning outcomes, cases, key terms and further references are added like a textbook.
- → Possible errors during the patient dealing and preventive measures to be naturally taken in all aspects are thoroughly discussed.
- → The future prospect of patient care pharmacists in diverse areas of health care elaborately discussed.
- → Discusses patient relationship management with a caring and compassionate touch which represent an extremely demanding approach to many high-profile healthcare settings.
- → Along with qualified professionals, undergraduate students can utilize this book as a reference for their courses like hospital and community pharmacy and pharmaceutics.
- → Scholars from countries around the world are announcing their favorable recommendation about the book.

Table 2: Comparison with Similar Available Books

Author	Title	Publisher	Price	Details	Superiority of Proposed Title
Richard Finkel	Patient Care Management Lab: A Workbook for Prescription Practice	Lippincott Williams & Wilkins, Feb 1, 2007	Kindle Edition 74 USD Spiral Bound: 47 USD	Develops and fine tunes pharmacy & pharmacy technician students' skills in reading, evaluating, and filling prescriptions.	Other than prescription handling, patient care pharmacists have many other responsibilities that are included.
Bernard J. Healey, Marc C. Marchese	Foundations of Health Care Management: Principles and Methods	John Wiley & Sons, Aug 9, 2012	E-book 72.99 USD Paperback 90 USD	The book covers such critical topics as leadership training, change management, conflict management techniques, culture building, quality improvement, and communications skills, as well as collaboration in the improvement of population health.	Patient care pharmacists need more coverage in areas of counseling, patient education, relationship management, understanding patient behavior, safety concerns, ethical issues and framework for safety in several stages of drug handling etc. are covered.
Seth B. Goldsmith	Principles of Health Care Management: Foundations for a Changing Health Care System	Jones & Bartlett Publishers, Oct 25, 2010	Paperback 192.95 USD	Hospital administration-based book, using relevant case studies to illustrate key points, this text explains the critical changes and challenges that administrators must deal	Pharmacists' role at every stages of patient handling is clearly defined along with the superiority of their services among other professionals in the healthcare arena.
Michael D. Hogue	The Pharmacist's Guide to Compensation for Patient-care Services	American Pharmaceutical Association, 2002	Paperback 249.01 USD	This comprehensive book covers all aspects of compensation for medication therapy management services provided by pharmacists in all practice settings	Other than pharmacists' compensation issues, every aspect pharmacy in patient care discussed deliberately as compensation of the professionals are not part of patient care.

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Gwen Marram Van Servellen	Communication Skills for the Health Care Professional: Concepts, Practice, and Evidence	Jones & Bartlett Publishers, Oct 7, 2009	Paperback $92.06, Kindle Edition $3.49	It provides future and practicing patient caregivers in all specialties and services with basic communication knowledge and skills and is an invaluable resource for those in administrative functions as well.	Along with communication, patient care pharmacists have to cover safety concerns, vigilance, drug and healthcare costing calculation, medicine reconciliation issues that are discussed giving similar priority.
Colleen Doherty Lauster, Sneha Baxi Srivastava	Fundamental Skills for Patient Care in Pharmacy Practice	Jones & Bartlett Publishers, 2013	104.95 USD	Drug related problems and counseling well discussed.	Along with drug related problems, patient problems, safety concerns, home care and long-term care are also discussed.
American Pharmacists Association	How to Implement the Pharmacists' Patient Care Process	American Pharmacists Association, 2015	78.07 USD,	Policy related book, aims to help pharmacists understand the components of the patient care process and apply the process to patients in all pharmacy practice settings. Six sample case studies set in different patient care settings enable the reader to practice applying the patient care process.	Patient care process discussed through issues like counseling, compliance, framework of safety, patient safety concern, cost saving and vigilance.
Thomas R. Brown	Handbook of Institutional Pharmacy Practice	American Society of Hospital Pharmacists, 2006	31.89 USD	An overview of health delivery systems and hospital pharmacy through various practice settings such as home care, long term care, hospice and palliative care, ambulatory care, and managed care this text focuses on various elements important to health-system pharmacies. The Handbook of Institutional Pharmacy Practice is the first step in developing a career in pharmacy and provides opportunities for study in career enhancement.	Many concepts of the proposed book resemble to Handbook of Institutional Pharmacy Practice but content is different. Moreover, studies discussed in proposed book are at least an era of advanced.
Kimberly S. Plake, Kenneth W. Schafermeyer, Robert L. McCarthy	McCarthy's Introduction to Health Care Delivery: A Primer for Pharmacists	Jones & Bartlett Publishers, 2016	46.93 USD	A Primer for Pharmacists, Sixth Edition provides students with a current and comprehensive overview of the U.S. health care delivery system, including social, organizational, and economic aspects, from the perspective of the pharmacy profession.	The book is far better than the proposed book but the book focuses on overall pharmacists' roles toward profession. The proposed book only focuses roles of patient care pharmacists and the content is different from McCarthy.

Author Profile

Author (*Figure 2*) completed B.Pharm (2004) and M.Pharm (2006) from Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka. He has completed his MBA (2007) from East West University. He was in faculty of Pharmacy, World University of Bangladesh as an Assistant Professor.

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Along with 8 years of teaching experience, he also worked for reputed pharmaceutical companies in strategic management for 5 years. He authored 11 books (*Table 3*) and many articles on alternative medicines, patient care, marine drug sources and other recent issues of healthcare in several journals (*Table 4*) and newspapers (*Table 5*). He is now acting secretary and treasurer in Dr. M. Nasirullah Memorial Trust.

Table 3: Author's Published Books

No.	Book	Publisher	Year Published	Role
1.	The Role of the Pharmacist in Patient Care	Universal-Publishers (US). (ISBN-10: 1627343083 ISBN-13: 9781627343084)	2020	Sole Author
2.	A Comprehensive Chemical and Pharmacological Review of Cosmetics	Nova Science Publishing Inc. (US), ISBN: 978-1-53618-571-3	2020	Sole Author
3.	A Review of Pharmaceutical Science	GRIN Verlag, 2020 (Munich, Germany) (ISBN 3346214184, 9783346214188)	2020	Sole Author
4.	Nature and Nutrition: A New Era of Therapeutic Herbs	Nova Science Publishing Inc. (US), (ISBN 9781536158922)	2019	Sole Author
5.	Non-drug pain management: opportunities to explore (e-Book)	BiomedGrid LLC, USA May 09, 2019 (ISBN: 978-1-946628-01-5)	2019	Sole Author
6.	Common GI Disorders & Alternative Measures (e-Book)	LAP LAMBERT Academic Publishing (ISBN-13: 978-613-9-47148-5)	2019	Sole Author
7.	A Comprehensive Review of Surgical Supplies (e-Book)	Peernest, US August 13, 2019 (ISBN: 978-1-946628-24-4)	2019	Sole Author
8.	Skin Aging and Modern Age Antiaging Strategies (e-Book)	Peernest, US July 23, 2019 (ISBN: 978-1-946628-23-7)	2019	Sole Author
9.	A Pharmacological Review of Sunscreens and Suntan Preparations (e-Book)	Peertechz Publications, India August 05, 2019 (ISBN: 978-81-943057-1-2, DOI: 10.17352/ebook10112)	2019	Sole Author
10.	Medicinal Values of Seaweeds (e-Book)	Academic Publications, India (ISBN: 978-81-943354-4-3)	2019	Sole Author
11.	Clinical Pharmacists in Chronic Care Management (e-Book)	Academic Publications, India (ISBN: 978-81-943354-0-5)	2019	Sole Author

Table 4: Author's Published Articles

No.	Publication	Journal	Citation
1.	Intermittent Fasting and Adding More days to Life (Letter to the editor)	Applied Clinical Pharmacology and Toxicology (ISSN: 2577-0225)	Mohiuddin AK (2019) Intermittent Fasting and Adding More Days to Life. Appl Clin PharmacolToxicol 3: 121. DOI: 10.29011/2577-0225.100021
2.	Pharmacist-Led Antimicrobial Stewardship	Lupine Online Journal of Pharmacology & Clinical Research	Abdul Kader Mohiuddin. Pharmacist-Led Antimicrobial Stewardship. LOJ Phar &Cli Res 1(4)- 2019. LOJPCR.MS.ID.000117. DOI: 10.32474/LOJPCR.2019.01.000117.
3.	Domination of Gastric Complications Among Diabetic Patients (Letter to the editor)	Journal of Gastroenterology and Hepatology Research	Mohiuddin AK. Domination of gastric Complications Among Diabetic Patients. Journal of Gastroenterology and Hepatology Research 2019; 8(4): 2928-2931. DOI: 10.17554/j.issn.2224-3992.2019.08.838

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100.	Phytochemical Screening & Biological Investigations of *FicusRacemosa*	Open Access Journal of Biogeneric Science and Research	Abdul Kader Mohiuddin*, SayraAkter Lia, Phytochemical Screening & Biological Investigations of *FicusRacemosa*. Op Acc J Bio Sci & Res 4(1)-2020. DOI: 10.46718/JBGSR.2020.03.000088

Table 5: Published Articles in Printed/Online Newspapers

No.	Publication	Journal	Citation
1.	নীরব ঘাতক ডায়াবেটিস: বাংলাদেশে বর্তমান পরিস্থিতি	দৈনিক সংবাদ বাংলা	আবুল কাদের মহিউদ্দিন. নীরব ঘাতক ডায়াবেটিস:বাংলাদেশে বর্তমান পরিস্থিতি. দৈনিক সংবাদ বাংলা/স্বাস্থ্য ও জীবন, জুলাই ১৯, ২০২০. https://www.dailycnbangla.com/print?id=1080
2.	কোভিড -১৯ এবং ২০টি সমাধান	আজ সারাবেলা	আবুল কাদের মহিউদ্দিন. কোভিড -১৯ এবং ২০ টি সমাধান. আজ সারাবেলা/ মত প্রকাশ, জুন ১, ২০২০. Available in: https://www.ajsarabela. com/2020/ 06/01/ কোভিড- ১৯-এবং-২০-টি-সমাধান.html
3.	মহামারী পরিস্থিতিতে টেলিফিল্মস	আজ সারাবেলা	আবুল কাদের মহিউদ্দিন. মহামারী পরিস্থিতিতে টেলিফিল্মস. আজ সারাবেলা/ মত প্রকাশ, মে ১৫, ২০২০. Available in: https://www.ajsarabela.com /2020/05/15/মহামারী- -টেলি.html
4.	Drug addiction, a consequence of social ills rather than individual flaws	The Independent	Abdul kader Mohiuddin. Drug addiction, a consequence of social ills rather than individual flaws. The Independent/Editorial, 27 November, 2019.
5.	Drug addiction: Causes and consequences	The Independent	Abdul kader Mohiuddin. Drug addiction: Causes and consequences. The Independent/Editorial, 4 December, 2019.
6.	Public health: Chemical residues in food grains	The Independent	Mohiuddin AK. Public health: Chemical residues in food grains. The Independent (OP-ED), 30 August, 2019.
7.	Risk-benefit issues of seafood consumption	The Independent	AK Mohiuddin. Risk-benefit issues of seafood consumption. The Independent, Op-ed, 19 September, 2019. Available in: http://www.theindependentbd.com/printversion/details/215966
8.	The diabetes TRACK and the track records	The Independent	AK Mohiuddin. The diabetes TRACK and the track records. The Independent, Op-ed, 02 November, 2019. Available in: http://www.theindependentbd.com/printversion/details/222026
9.	Health hazards with adulterated spices: Save the 'onion tears'	The Independent	Abdul Kader Mohiuddin. Health hazards with adulterated spices: Save the 'onion tears. The Independent (Op-ed), 22 November, 2019
10.	In search of an effective programme for dengue prevention	The Independent	AK Mohiuddin. In search of an effective programme for dengue prevention. The Independent, 04 September, 2019.

III. Conclusion

Universal-Publishers eagerly seeks prolific authors who correctly are leading experts in their chosen field, and whose work addresses a specialized audience. Their mission is to expose novel ideas and important scholarship. In exchange for distribution rights, they offer vital distribution, adequate compensation, multiple media editions, and personal attention. The esteem book was under editing and improvisation from the beginning of the year 2019, after

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copyright agreement signing. The published book is eligible to provide learning to both Pharmacy apprentices (mainstream and diploma pharmacists) for their established courses related to Hospital and Community Pharmacy, Pharmacy Compounding and Dispensing as well as to the allied health professionals who are close to ill patients in their day-to-day activities. Significant limitation of the book lies with the continuous improvement in various aspects of healthcare services around the world that cannot be detailed in a particular frame. However, further reading references are given so that an aware reader can have an idea of credible sources that can undoubtedly benefit their future learnings. Also, a comparison table is added in *Annexure 26 of the said book (Table 2 of the article*), showing a few points that makes the book superior to similar other available books, which is further mentioned that those books obviously have their unique superiority over this book, *The Role of the Pharmacist in Patient Care* (*Achieving High Quality, Cost-Effective and Accessible Healthcare Through a Team-Based, Patient-Centered Approach*) in terms of their focus on respective subject matter(s). The book solely claims its superiority in terms of focus in detailing Pharmacists' major roles and responsibilities in patient care.

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Sample Chapter:
https://www.docdroid.net/HPCzPeD/sample-chapter-patient-care-pdf

List of Contents (with sub-headings)
https://www.docdroid.net/WmUgghH/chapter-contents-docx

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Cytokine Storm: A Suicidal Immune Response to Novel Corona Virus

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Abstract- SARS-CoV-2 virus is responsible for the COVID-19 disease in patients. Only 15-20 % of COVID-19 patients have developed severe pulmonary symptoms and illness, which are fatal to patients. Hyper-immune response to the SARS-CoV-2 virus by the host's immune system causes the release and over production of certain kinds of inflammatory mediators and cytokines. And it results in the cytokine storm. Cytokine storm produces the hyper inflammatory reaction, which deteriorates the cells and tissue. This type of immune response is host killing and suicidal response to the SARS-CoV-2 virus by the host. This suicidal response ultimately leads to lung damage, respiratory tract pneumonia, ARDS, multi-organ failure at a later stage and ultimately death. Hence, it needs to suppress the hyper-functioning of the immune system to inhibit the cytokine release and cytokine storm. Anti-inflammatory and immuno-modulatory drugs can be repurposed to manage the cytokine storm and hyper-immune response. Inhibition and management of the host's suicidal immune response and cytokine storm, could be life-saving and reduce the mortality rate in COVID-19 patients.

Keywords: *sars-cov-2; covid-19; cytokine storm; hyperimmune response; ards; multi-organ failure; drugrepurposing.*

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CASE STUDY

Cytokine Storm: A Suicidal Immune Response to Novel Corona Virus

Jignakumari J. Gohil [α] & Chiragkumar J. Gohil [σ]

Abstract- SARS-CoV-2 virus is responsible for the COVID-19 disease in patients. Only 15-20 % of COVID-19 patients have developed severe pulmonary symptoms and illness, which are fatal to patients. Hyper-immune response to the SARS-CoV-2 virus by the host's immune system causes the release and over production of certain kinds of inflammatory mediators and cytokines. And it results in the cytokine storm. Cytokine storm produces the hyper inflammatory reaction, which deteriorates the cells and tissue. This type of immune response is host killing and suicidal response to the SARS-CoV-2 virus by the host. This suicidal response ultimately leads to lung damage, respiratory tract pneumonia, ARDS, multi-organ failure at a later stage and ultimately death. Hence, it needs to suppress the hyper-functioning of the immune system to inhibit the cytokine release and cytokine storm. Anti-inflammatory and immuno-modulatory drugs can be repurposed to manage the cytokine storm and hyper-immune response. Inhibition and management of the host's suicidal immune response and cytokine storm, could be life-saving and reduce the mortality rate in COVID-19 patients.

Keywords: sars-cov-2; covid-19; cytokine storm; hyperimmune response; ards; multi-organ failure; drug-repurposing.

I. Introduction

A novel corona virus named "Severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2) was identified in 2019-2020 as a causative agent of several acute respiratory illness/infection [1]. This disease is caused by SARS-CoV-2, termed as "Coronavirus Disease 2019" (COVID-19). Covid-19 is a worldwide pandemic.

As theSARS-CoV-2 virus infects the cell, it copies itself very quickly. But the pathogenesis of the disease is still unclear. Because it produced a varying degree of clinical symptoms and illness in the various patients. In some of the patients, it only causes the asymptomatic forms and mild illness, while in some patients causes the fatal and life-threatening illness.

Among all COVID-19 patients, most of the patients are mildly affected and non-symptomatic. Some of the patients having mild symptoms like cough, fever, and muscle soreness. These types of patients, which are having mild symptoms at the early stage got severe to chronic illness and symptoms in the later stage of the disease or during the recovery process. The majority of critically ill patients did not develop severe clinically fatal complications in the early diseased stage.

Approximately 15-20 % of the COVID-19 patients have developed pulmonary symptoms such as breathing difficulties and require hospitalization [2, 3]. In hospitalized patients, some of the patients show Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure within 48-72 hours [4]. During the chronic illness stage, the ARDS and multiple organ failure occurs rapidly. These result in the death of the patients in a short time [5].

a) *Markers of COVID-19*

There is a reduction in the absolute lymphocyte count as well as a relative increase in neutrophil-lymphocyte ratio (NLR) in COVID-19 patients.

Elevation in C-reactive protein (CRP) and ferritin is also common.

Other markers of coagulation and organ damage such as D-dimer, lactate dehydrogenase (LDH), creatinine and bilirubin are also observed to be elevated.

b) *Hyperimmune Response*

This is the question for the healthcare providers across the world, why only certain COVID-19 patients are having a chronic illness and severe symptoms. The answer is the hyper-immune response by the patient's immune system to the SARS-CoV-2 virus [5].

In many patients, the fatal damage has been occurred by the deranged or hyper immune response to the SARS-CoV-2 virus, rather than the virus itself. In many of the COVID-19 patients, their immune response has been as/more destructive as the virus that causes the disease.

It is seen the lung damage, severe respiratory damage and persistent high fevers in some critically ill COVID-19 patients. These are signs of hyper immune response and over functioning of the immune system.

Hyper-immune response induces the release of inflammatory proteins and mediators. Clinical studies show that a high level of immune system proteins has been found in the blood of the many seriously ill COVID-19 patients.

Hence, it is clear that the release of these cytokines by the COVID-19 patient's immune system is

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responsible for the severe life-threatening clinical condition. Cytokine induces the aggravation of the disease and ultimately results in the cytokine storm.

Amount and levels of released cytokines in the cytokine storm; are injurious to host cells. This clinical condition is called disseminated intravascular coagulation (DIC) and it leads to a multi-organ system dysfunction. Cytokine storm is responsible for the ARDS and multiple organ failure in the stage of the chronic illness [7].

Along with the COVID-19, hyper-immune response and release of immune cytokine proteins have been also occurring in some clinical conditions like: In infections like flu, H1N1 influenza, during certain kinds of cancer treatments (chemotherapy), and in autoimmune diseases (juvenile arthritis).

Clinical data evidence that; the amount of the cytokines produced by cells in response to a SARS-CoV-2 infection is about 50 times higher than the number of cytokines produced in response to West Nile virus or Zika virus infections.

Cytokine storm generally observed in the cytomegalovirus, Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis, group A streptococcus, influenza virus, variola virus and in the SARS-CoV-2 virus [8].

II. Cytokines and Cytokine Storm

Cytokine was first time coined in the context of avian H5N1 influenza virus infection in 2005 [9]

The word cytokines composed of two words, “Cyto (cell)” and “Kines (small proteins)”. Cytokines are an essential part of the inflammatory process. Cytokines are a diverse group of the protein which are being secreted by the immune cells. Cytokines are produced by certain types of immune cells like macrophages, dendritic cells, natural killer cells, T and B lymphocytes. Cytokines have an autocrine, paracrine, and/or endocrine activity. And it can elicit a wide range ofresponses (through receptor binding) depending upon the types of cytokine and target cell [10].

The principal role of the cytokine is intercellular signaling and communication. The main functions of cytokines are control of cell proliferation and differentiation, regulation of angiogenesis and immune and inflammatory responses. Apart from these, it also performs various functions in the body.

a) Cytokine Storm

Cytokine storm has defined by hyperactive immune-response to SARS-CoV-2 virus by the host’s immune system. It consists of the release of interferons, interleukins, tumor-necrosis factors, chemokines, and several other mediators [11].

These released soluble markers of inflammation are certain kinds of proteins of the immune system, called cytokines. These mediators are part of a well-conserved innate immune response, which is necessary for the efficient clearance of virus and infectious agents Generally, the anti-viral immune response requires the activation of the inflammatory pathways of the immune system. If this immune response remains uncontrolled, the hyper immune response can cause severe clinical manifestation [12].

i. *Mechanism*

When the immune system (macrophages and some other kinds of immune cells) of the host/patient detects the antigen of the SARS-CoV-2virus, they send the messages by releasing various proteins (cytokines). This immune response to the SARS-CoV-2 virus initiates the sequence of events results in the recruitment of leukocytes and plasma proteins (cytokines) to the site of infection [13].

These cytokines will produce and release the other immune cells to initiate an inflammatory response. This inflammatory immune response which is initiated by the cytokines helps the body to fight against the SARS-CoV-2virus [14].

When the host’s immune system hyper reacts to the SARS-CoV-2 virus, macrophages can also release other signaling molecules (catecholamines). These catecholamines trigger the release of more cytokines and intensify the inflammatory response. Systemic hyper-inflammation elevates the level of various cytokines such as TNF, IL-2, IL-7, IL-6, IP-10, IFN-γ, MIP1α, MIP1β and MCP1. Ultimately there is a large amount of the cytokines release in the COVID-19 patient. This flux of the cytokines is known as a “Cytokine storm”.

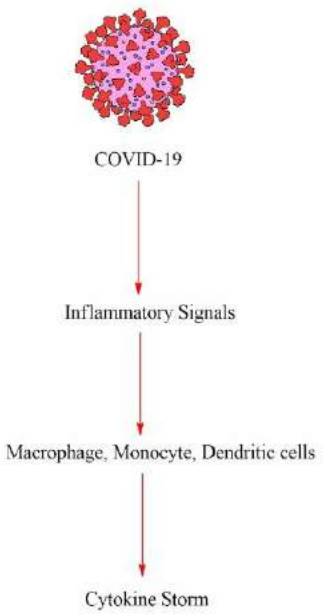


Figure 1: Hyperimmune response and Cytokine Storm[15]

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These clinical conditions and responses are referred to as macrophage activation syndrome, cytokine release syndrome or simply cytokine storms.

Il-1, TNF-a, and IL-6 are the main pro-inflammatory cytokines in the immune response to the SARS-CoV-2 virus. In turn, an increase in the level of these three cytokines also induces the adhesion of the macrophages, neutrophils, and T cells from the circulation into the site of infection. This cascade of mechanisms produces destructive effects on human tissue. And causes the destabilization of endothelial cell to cell interactions, damage of vascular barrier, capillary damage, diffuse alveolar damage. Cytokine storm induces lung injury [16]. And if the cytokine storm is not controlled and left untreated, then patients will have ARDS as a result of acute lung damage followed by multi-organ failure and death.

III. Role of Interleukins in Cytokine Storm

Previously, it was thought that Interleukins are the cytokines that are produced by the leukocytes. But now, it is clear that interleukins are produced by a wide variety of cell types.

In contrast to the IFNs, the interleukins are a diverse family of immune system regulators. Their main role is in immune cell differentiation and activation. The prime role of the interleukins is in intercellular communication [17]. They also control the growth and differentiation of the leukocytes. As of the other cytokines, it elicits the wide range of the response [18].

In the interleukin family, IL-1 and IL-6 are pro-inflammatory cytokines. It mediates the host's immune response to SARS-CoV-2 virus infection through direct and indirect mechanisms [19]. Receptor signaling of IL-1 is responsible for acute lung immunopathology in COVID-19patients [20].

a) Crucial Role of IL-6

Interleukin-6, a pro-inflammatory cytokine, is a key mediator in the acute inflammatory response and the purported cytokine storm. Increased level of IL-6 in the serum have been correlated with respiratory failure, ARDS and adverse clinical outcomes [21].

IV. Cytokines Storm and Lung Damage

Many studies have been carried out to find; whether drugs and treatment of COVID-19 provoke the cytokine storm or not.

Cytokine storm is the situation of the hyper immune response to the antigen, where the body starts attacking its own cells and tissues rather than fighting off the antigen (virus) [22].

Cells kill themselves (suicidal response); when they sense the antigen or virus enters the cells and begin to infect them. This type of self-killing response is a protective mechanism, so the virus does not spread to the other cells [23].

When the cells can't cope up with the antigen/virus they begin to send SOS signals through immune proteins and chemical messengers. These immune proteins and chemical messengers are a certain type of cytokines. The release of cytokines triggers cell death. A large number of virus-infected cells release the cytokines at the same time, so a larger number of tissues can die. In COVID-19 patients, this phenomenon is mostly seen in the lung tissues [24].

This hyper-inflammatory condition consists of the pulmonary infiltration and exudation, organ damage and dysfunction of coagulatory pathways, which leads to the worsening of oxygen saturation.

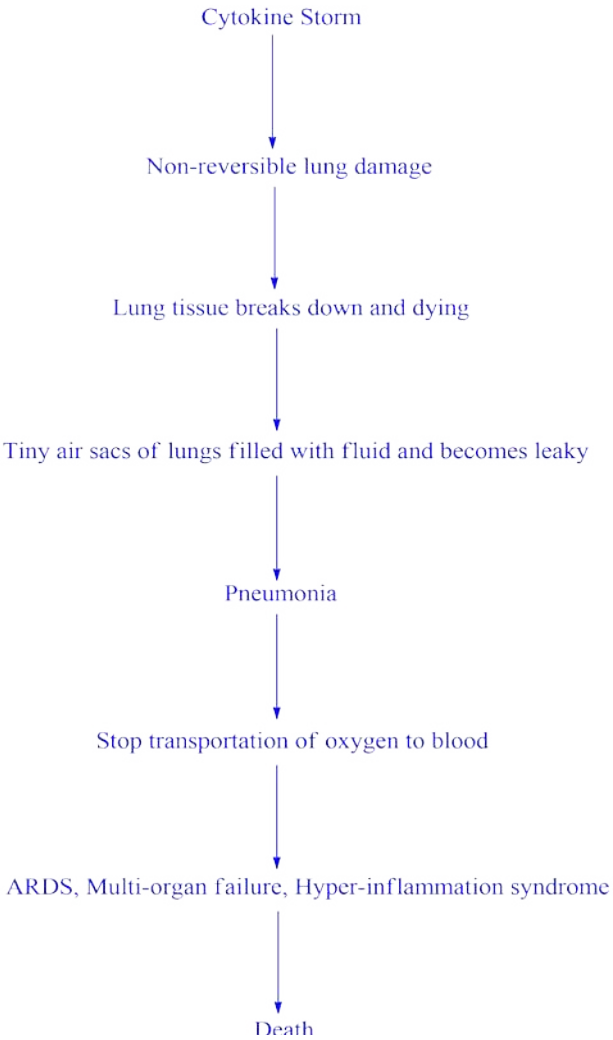


Figure 2: Lung damage by Cytokine storm [25]

Cytokines and chemical mediators eat away at the lung and the lung becomes greatly damaged, in a non-reversible manner. As the lung's tissue starts dying and breaks down, the lung's wall (tiny air sacs) is filled with the fluid and becomes leaky. So, this causes pneumonia and stops the transport and supply of

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oxygen to the blood and body. Hence, the body will be starving of oxygen and respiratory distress syndrome follows. Then other organs start to fail.

This clinical condition plays a central role in the death of a large number of COVID-19 patients.

V. Treatment of Cytokine Storm

Cytokine Storm (CS) is a lethal clinical condition, and it requires intensive care; since it is responsible for the high mortality rate in COVID-19 patients [26, 27].

As cytokine storm is a chronic inflammatory condition induced by the hyper immune response of the host, the inflammation must be treated and control to cope the condition.

Basically, anti-inflammatory drugs, a combination of immune-modulators, and some other drugs can be used. IL-6 inhibitors and high dose corticosteroids block pathways critical to host immune responses. Many monoclonal antibody drugs are being repurposed from treating patients with chronic inflammatory conditions [28, 29].

a) Catecholamine inhibitors

Before the cytokine storm, the circulating level of catecholamines increases rapidly in the COVID-19 patients. This catecholamine is responsible for the cycle of inflammation and cytokine storm. If we inhibit the release of the catecholamine, we can inhibit the cytokine storm. We can use and test the catecholamine inhibitor drugs to treat COVID-19 patients.

b) Alpha-blockers

Various studies on mice and other findings show that the alpha-blockers can be used to break the hyper-inflammatory chain reaction. So, we can prevent it from converting to cytokine storm. Generally, alpha-blocker drugs are used for the treatment of prostate disease and high blood pressure.

i. *Mechanism of action*

Cell signaling and communication have occurred through the cytokines and chemical mediators. Alpha-blocker drugs interfere with this cell signaling during the inflammatory immune response and inhibitit. Alpha-blockers break the chain of cytokine release and inhibit the cytokine storm.

Data indicate that, COVID-19 patients taking the regular and gradual dose of an alpha-blocker (prazosin) have no sign of the hyper inflammatory immune response or cytokine storm.

c) Anti-rheumatic drugs

Another approach to control the hyper-inflammatory immune response is to use anti-rheumatic drugs..

In a study, COVID-19 patients are treated with I.V infusions of "Actemra (anti-rheumatic)". In these patients, actemra drug blocks the cytokine IL-6 receptor and decreases the circulating level of IL-6. So actemra successfully inhibits the cytokine storm in COVID-19 patients. These results encourage the researchers to test another anti-arthritis drug names "auranofin".

d) Chloroquine and Hydroxy-chloroquine

Chloroquine and hydroxychloroquine have a variety of biological activity from antimalarial, antiviral to anti-inflammatory. Because of the anti-inflammatory property, they are used in the therapy of autoimmune diseases.

Cytokine storm is a similar condition to the autoimmune disease. So these drugs can be effective in the management of the cytokine storm in the COVID-19 patients.

i. *Mechanism of action*

Chemically, chloroquine; and hydroxychloroquine are weak bases in nature. So they used to accumulate in acidic organelles like lysosomes. And they increase lysosomal/endosomal pH. So, chloroquine and hydroxychloroquine can decrease the production of various pro-inflammatory cytokines. Therefore, prevent the cytokine storm [30] and inhibit replication of the SARS-CoV-2 virus [31].

e) Corticosteroids

Corticosteroids can be used as an anti-inflammatory drug in COVID-19 patients. Corticosteroids down-regulate the hyper-activity of the immune system and inhibit the release of the cytokine and cytokine storm.

Corticosteroids are most widely used in the treatment of many infectious diseases. But, the use of corticosteroids drugs in the treatment of COVID-19 can cause host immune suppression and delay of viral clearance.

f) IL-6–IL-6R antagonists

IL-6 is a potential target in the treatment of cytokine storm because IL-6 plays the central role in the cytokine release and hyper-inflammatory cytokine storm. Many studies have been carried out using the IL-6–IL-6R antagonist drugs to treat COVID-19 patients. Treatment with IL-6–IL-6R antagonists drugs shows that; drugs inhibit the cytokine chain reaction And decreases the level of the pro-inflammatory cytokine IL-6. In turn, a fall in the circulating level of the cytokines. Hence, inhibiting the cytokine storm. And shown a good patient prognosis.

g) Monoclonal antibody

Elevated levels of the IL-6 in the blood of COVID-19 patients; have been reported to be predictive of a lethal outcome in patients [32].

Therefore, it needs to be harnessed the increasing level of Il-6 in the COVID-19 patient to prevent the cytokine storm and to save a patient's life. In this

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situation, a monoclonal antibody can be used to block the IL-6.

i. *Tocilizumab*

Tocilizumab is a recombinant humanized monoclonal antibody; and it is an IL-6 receptor antagonist.

Tocilizumab (specific monoclonal antibody) therapy has been used to treat the cytokine storm and critically ill patients with extensive lesions in bilateral lungs and a confirmed elevated level of IL-6.

Elaborate studies on 20 severe patients of COVID-19 indicate that the tocilizumab drug effectively blocks IL-6. And it leads to a reduction in fever and lung lesion opacity; and recovered the percentage of lymphocytes in peripheral blood [33].

On the other hand, there is a risk of opportunistic infections like tuberculosis, fungal, and other viral infections caused by anti-IL-6 monoclonal antibodies.

ii. *Itolizumab*

Itolizumab is an immune-modulator drug. Itolizumab is an anti-CD6 humanized IgG1 monoclonal antibody (mAb). It can potentially inhibit the cytokine storm and is found as a life-saving drug in COVID-19patients.

It is an approved drug for the treatment of psoriasis in India [34, 35].

- *Mechanism of action*

It binds with T-effector cells through domain-1 of the CD6 receptor present on it. Domian-1 of T-effector cells is responsible for priming, activation, and differentiation of T-Cells [36].

Itolizumab's binding blocks the co-stimulation pathway and leads to inhibition of proliferation of T-cells. It consequently reduced the level of pro-inflammatory cytokines (IL17A, TNF-α, IL-6, IFN-γ, and IL-2). And brings down the release of multiple cytokines and cell signaling transduction and inhibits the cytokine storm.

After the whelming result in a study on COVID-19patients, it is under clinical trials to treat COVID-19.

VI. Conclusion

The immune system of some COVID-19 patients gives a suicidal immune response to the SARS-CoV-2 virus. Which excessively release inflammatory cytokines and proteins.

The high circulatory level of cytokines known as a cytokine storm; initiates the chronic inflammatory reaction in the body (mostly in the lung). Cytokine storm leads to physiological deterioration of the lung tissue and causes ARDS, multiple-organ dysfunction, and death.

Particular pro-inflammatory cytokine IL-6 is the marker of the cytokine storm. The blood level of the IL-6 is correlated with cytokine storm in the body. The normal level of the IL-6 in the blood is <7, an IL-6 level more than 7 indicating the cytokine storm.

So timely control of the cytokine storm in its early stage would be beneficial and can save the patient's life.

Corticosteroids, anti-rheumatoid drugs, and many other anti-inflammatory drugs have been repurposed to treat the cytokine storm and hyper inflammatory condition inCOVID-19 patients. The use of newer IL-6 inhibitors/antagonist drugs has also been proved effective in the treatment of the cytokine storm.

Target-specific monoclonal antibody drugs have been used to decrease the hyper-functioning of the patient's immune system. These humanized monoclonal antibody drug show impressive results in the management of severe clinical conditions in the patients.

Currently there are no approved drugs and therapies available for the treatment of COVID-19 patients. Several marketed drugs have been repurposed for the treatment of cytokine storm. And many immune-modulator biologics have been used off label for the management of the hyper/suicidal immune response in the COVID-19 patients.

All the results of these new monoclonal antibody drugs are preliminary. There are no randomized clinical trials of the newer monoclonal antibody drugs that have been published to date, so it requires clinical trials and confirmatory studies to evaluate its role in COVID-19 therapy.

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Note

SARS-CoV-2 virus and Novel Corona Virus, both the terms are similar.

Author Contributions

Dr. Jignakumari J. Gohil contributed to providing clinical data of COVID-19 patients.

Co-author, Chiragkumar J. Gohil contributed to writing, editing, and revising of the manuscript.

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The Effect of Virechana with Manibhadra Churna in Psoriasis - A Case Study

By Maneesha. P.C & Shaiju Krishnan
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Abstract- Panchakarma is referred as penta-biopurificatory process. Virechana Karma is one among Panchakarma; by which orally administered drug acts on internal Dosha especially Pitta Dosha and expel them out of the body through Guda. Psoriasis is a common chronic skin disorder of autoimmune origin. A 42 year old male patient c/o itching overhead, behind the ears, nails, lower back and legs since 2 years and while itching he gets whitish powder. He has consulted a dermatologist and has taken modern medicine. He got symptomatic relief. As soon as he stops medicines, the condition worsens and reoccurrence of disease was going on. Meanwhile severe burning sensation on chest was also happened. So he has planned to take Ayurveda treatment for the same. There was no history of any systemic illness. The present case was diagnosed as psoriasis from a detailed history taking and clinical examination. A positive family history was noted. A classical way of Virechana Karma was planned with Manibhadra Churna. After Virechana, Samyaka Shudhi Lakshana was achieved; symptoms such as itching, erythema, scaling, candle grease sign and Auspitz sign were not found. Reoccurrence of disease was not found even after 2nd follow up.

Keywords: virechana, psoriasis, manibhadra churna, kushta.

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The Effect of Virechana with Manibhadra Churna in Psoriasis – A Case Study

Maneesha. P.C [α] & Shaiju Krishnan [σ]

Abstract- Panchakarma is referred as penta-biopurificatory process. Virechana Karma is one among Panchakarma; by which orally administered drug acts on internal Dosha especially Pitta Dosha and expel them out of the body through Guda. Psoriasis is a common chronic skin disorder of autoimmune origin. A 42 year old male patient c/o itching overhead, behind the ears, nails, lower back and legs since 2 years and while itching he gets whitish powder. He has consulted a dermatologist and has taken modern medicine. He got symptomatic relief. As soon as he stops medicines, the condition worsens and reoccurrence of disease was going on. Meanwhile severe burning sensation on chest was also happened. So he has planned to take Ayurveda treatment for the same. There was no history of any systemic illness. The present case was diagnosed as psoriasis from a detailed history taking and clinical examination. A positive family history was noted. A classical way of Virechana Karma was planned with Manibhadra Churna. After Virechana, Samyaka Shudhi Lakshana was achieved; symptoms such as itching, erythema, scaling, candle grease sign and Auspitz sign were not found. Reoccurrence of disease was not found even after 2nd follow up.

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I. Introduction

Proper Shodhana Karma brings Roga Apunarbhavatwam[1]; that means the disease never reoccur. If we speak practically, reoccurrence of disease can be delayed for longer period .Shodhana Karma helps in detachment of Doshas from their root. Panchakarma is also referred as penta-biopurificatory process. Virechana Karma is one among Panchakarma; by which orally administered drug acts on internal Dosha, especially Pitta Dosha and expel them out of the body through Guda. Virechana is the prime treatment for Pittaharana and Amashayagata Pitta[2]. Psoriasis is a common chronic skin disorder of autoimmune origin. The exact cause of the condition is not known. But it is believed that the main culprit behind the pathology may be the autoimmune response of T-lymphocytes and neutrophils which causes the over production of healthy skin cells which rapidly moves to the outermost layer of the skin in days causing a build-up of thick, scaly patches on the skin surface. It is also believed that genetic factor also plays an eminent role in this condition.

In modern medicine, the mild form of this condition is managed by topical agents like corticosteroids, moisturisers etc. Moderate condition is managed by phototherapy. For severe conditions systemic agents like methotrexate, ciclosporin, hydroxyl carbamide etc. are used. Still the condition is usually reoccurred within months.

The word Psoriasis is from the Greek word psōra meaning "itch", psoriasis is a chronic, non-contagious disease characterized by inflamed lesions covered with silvery-white scabs of dead skin[3].Normal skin cells mature and replace dead skin every 28-30 days. Psoriasis causes skin cells to mature in less than a week. Because the body cannot shed old skin as rapidly as new cells are rising to the surface, raised patches of dead skin develop on the arms, back, chest, elbows, legs, nails, folds between the buttocks, and scalp[3]. Psoriasis is considered mild if it affects less than 5% of the surface of the body; moderate, if 5-30% of the skin is involved, and severe, if the disease affects more than 30% of the body surface[3].

From the available studies, the prevalence of psoriasis in India ranges from 0.44 to 2.8% [4]. In another study it is found that point prevalence of psoriasis is 8% [5].The same study has described that among the psoriasis patients, the ratio of male to female was 1.1:1. Highest prevalence was noted in the age group of 21-30 and 41-50 years[5].

II. Definition

Psoriasis is a non-infectious chronic inflammatory disease of the skin, characterised by well-defined erythematous plaques with silvery scale with predilection for the extensor surface and scalp and a chronic fluctuating course[6].

III. Types of Psoriasis

Dermatologists distinguish different forms of psoriasis according to which part of the body is affected, how severe symptoms are, how long they last, and the pattern formed by the scales.

The most common one is chronic plaque psoriasis (50%); the most common sites of involvement in descending order of frequency were the palms and

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soles (33%) and scalp (20.8%); nearly 4.1% presented with erythroderma[5].

Plaque psoriasis[7]- the most common type. Lesions are well demarcated, red with dry, with a silvery-white scale. The elbows, knees and lower back are commonly involved. Other sites of predilection include scalp, nails, flexures and palms.

Guttate psoriasis[7] – commonly seen in children and adolescents and may follow a streptococcal sore throat.

Erythrodermic psoriasis[7] – skin becomes universally red or scaly. As in other forms of erythroderma temperature regulation becomes problematic with hypothermia or hyperthermia.

Pustular psoriasis[8] – there are two varieties; generalised form and localised. It is characterized by blister-like lesions filled with non-infectious pus and surrounded by reddened skin. Generalized pustular psoriasis can make life-threatening demands on the heart and kidneys.

Palomar-plantar pustulosis (PPP) causes large pustules to form at the base of the thumb or on the sides of the heel. In time, the pustules turn brown and peel.

In Ayurveda, psoriasis can be correlated to many varieties of Kushta; such as Sidhma Kushta, Ekakushta, Kitibha Kushta, Mandala Kushta etc. due to similarity of signs and symptoms. The present case is correlated to Sidhma Kushta. Acharya Charaka explained Sidhma under Mahakushta. Sushruta and Vagbhata Acharya described it under Kshudra Kushta. In this case study, Sweta (whitish), Tamra (coppery), Alabu Pushpa Varna (pinkish) and Rajo Brushtam Vimunchati (peeling of skin) features of Sidhma were found. It is Vatakapha predominant disease. In every Kushta, Dooshana of Sapta Dravya (Tridosha, Twak, Rakta, Mamsa and Lasika) occurs. Kushta is difficult to cure, but in classics repeated Shodhana Karma has been advised without harming Prana of Shareera[9]. In Vata predominant condition Sarpipana is administered. In Pitta predominant cases Raktamokshana and Virechana are done. Whereas in Kapha dominant condition Vamana Karma is followed[9].

Aim

To evaluate the effect of Virechana Karma in Psoriasis.

Objective

To evaluate the effect of Virechana Karma with Manibhadra Churna in Psoriasis.

Place of Study

This case study was done in the department of Panchakarma, MVR AMC, Parassinikadavu, Kannur.

IV. Case Study

a) Presenting complaints

A 42 year old male patient c/o itching overhead, behind the ears, nails, lower back and legs since 2 years and while itching he gets whitish powder.

b) History of presenting complaints

Patient was apparently normal before 2 years; gradually he developed itching over his head. He has consulted a dermatologist and has taken modern medicine. He got symptomatic relief. After 2months, again itching was started on head and leg associated with severe burning sensation on chest. Again he has taken modern medicine for the same and got relief. But all the symptoms were remitted as soon as the medicines were stopped. So he has planned to take Ayurveda treatment for the same.

c) History of previous illness

Nothing specific
N/c/o DM, Hypertension or any systemic illness.

d) Personal History

B - constipated, irregular
M - 6 to 7 times per day
A - decreased
S - disturbed
Diet - mixed
Addiction - tea (~10 times/day)

e) Family History

Positive family history

f) General Examination

BP – 130/90mmHg
Pulse – 83/min
RR – 16/min
HR – 83/min
Temp. – 97.4^{0}F
Weight – 72Kg
Height – 165cm
BMI –26.45Kg/m^2

g) Ashtashana Pareeksha

Nadi – Sadharanam
Mutram – Anavilam
Malam – Badha
Jihwa – Upaliptam
Drik – Prakruta
Sparsha – Anushnasheeta
Shabda – Spashta
Akruti – Madhyama

h) Dashavidha Pareeksha

1) Dooshya
Dosha – Vatakapha
Dhatu – Rasa, Rakta, Mamsa
Mala – Sweda

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2) Desha
Bhumi – Jangalam
Deha – Sarvashareera
3) Bala
Rogibala – Madhyama
Rogabala – Madhyama
4) Kala
Kshnadi – Sharadkala
Vyadhyavastha – Vyakta
5) Analam – Vishamagni
6) Prakruti – Pittakapha
7) Vaya - Youvanam
8) Satwam – Madhyama
9) Satmyam – Sarvarasa
10) Koshta – Krurakoshta

i) Systemic examination
RS – Normal
CVS – S_1S_2 heard
P/A – Soft, non-tender

j) Skin examination
General inspection of skin – lesion present on scalp, ears, nails, lower back and legs
Skin colour – pinkish
Inspection of lesion – plaque, symmetrical, hard surface, well demarcated
Palpation – roughness, scaly lesion
Koebner's phenomenon – positive
Auspitz sign – positive
Candle grease sign – positive

k) Diagnosis

On the basis of detail clinical history and examination, the present case was diagnosed as Plaque Psoriasis.

l) Assessment Criteria

1) Itching

Score	Symptom
0	No itching
1	Mild itching
2	Moderate itching
3	Severe itching

2) Erythema

Score	Symptoms
0	No erythema
1	Mild erythema
2	Erythema without oedema
3	Erythema with oedema
4	Erythema with oedema and blisters

3) Scaling

Score	Symptoms
0	No scaling
1	Mild scaling from some lesion
2	Moderate scaling from some lesion
3	Severe scaling from some lesion
4	Severe scaling from all lesion

4) Thickness

Score	Symptoms
0	No thickness
1	Mild thickness
2	Moderate thickness
3	Very thick
4	Very thick with in duration

5) Candle grease sign

Score	Sign
0	Absent
1	Improved
2	Present

6) Auspitz sign

Score	Sign
0	Absent
1	Improved
2	Present

Ethical approval: A written consent was taken from the patient.

m) Treatment protocol

1) Rukshana Chikitsa (Abhyantara and Bahya)
- Panchakola Churna (5g) with Takra for 5days (B/F, twice daily)
- Udwartana with Nimba Churna and Aragwadha Churna

2) Snehana Karma (Abhyantara and Bahya)
- Snehapana with Aragwadha Mahatiktakam Grita in Aarohanakrama Matra until Samyak Snigdha Lakshana has obtained. In this case for 7days (30ml, 60ml, 90ml, 120ml, 150ml, 170ml, 200ml).
- Abhyanga with Psoricure oil and Bashpa Sweda for 3days

3) Shodhana Karma
- Virechana with Manibhadra Churnam (50g) with lukewarm water, given at 8am.

4) Samsarjana Karma
- Peyadi and Rasa Samsarjana Krama administered for 8 Annakala (5days)

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5) Shamana therapy

- Panchatikta Guggulu Grita 10ml (B/F, Morning only)
- Psoricure oil (External application) weekly once
- Avipatti Churna 15g with hot water (weekly once, night only)

All the medicines were prepared as per classics in the pharmacy of MVR AMC, Parassinikadavu, Kannur.

n) Assessment Criteria of Virechana

Aantiki Shudhi – Kaphantam
Vaigiki Shudhi – 20 Vega
Laingiki Shudhi – Laghutwam, Indriya Prasada, Agni vardhana, Kramat Vit, Pitta, Kapha and Anila Pravrutti.
Manika Shudhi – 3 Prastha

V. Results

During Snehapana itching, roughness of lesion and scaling were reduced. After Virechana Karma Samyaka Shudhi Lakshana was achieved; symptoms such as itching, erythema, scaling, thickness, candle grease sign, Koebner's phenomenon and Auspitz sign were not found. The weight of the patient was also reduced.0

Signs & Symptoms	Before Treatment	After Treatment
Itching	3	0
Erythema	3	0
Scaling	4	0
Thickness	3	0
Candle grease sign	2	0
Koebner's phenomenon	present	absent
Auspitz sign	2	0
Weight of the patient	72kg	67kg

After the follow up period of 6 months the patient was fine and reoccurrence of the disease was not found. So all the Shamana medicines were stopped. One more follow up was planned again after 6 months. Patient was fine and no reoccurrence of the condition was happened.



Fig. 1: BT & AT



Fig. 2: BT & AT

VI. Discussion

Kushta is noted as Dush Chikitsya due to Prasarana Bhava. Raktadhatu is the main reason for Prasarana Bhava. Pitta and Rakta are Ashraya-Ashrayee Bhava; hence Virechana Karma can bring best result. In the present case study, the patient is Dushchardya too. So Virechana Karma was planned. Agni was deranged in the patient. So Deepana – Pachana Karma before Snehapana was advised. Panchakola Churna was taken 5gm with half glass of Takra; which is Shreshta Pachana and Deepana Dravya. Thus, internal Ama Pachana was brought out and Jadharagni was kindled. For external Rukshana purpose, Udwartanam with Nimba Churna and Aragwadha Churna was done. Nimba (*Azadiractaindica*) and Aragwadha (*Cassia fistula*) are anti-fungal, anti-bacterial and anti-pruritic drugs. Udwartana helped in the exfoliation of dead tissues.

Arohanakrama Snehapana with Aragwadha Mahatiktaka Grita was given for 7days. Samyak Snigdha Lakshana such as Vata Anulomata, Agni Deepti, Snigdha Vit, Twak Snigdhata was obtained. In order to pacify Kapha and promote easy evacuation of Doshas with stools, 3days Vishrama Kala was planned. In these 3days Abhyanga with Psoricure oil and Bashpa Sweda were done. Next day Virechana was administered with Manibhadra Churna 50g in lukewarm water at 8am. It is the drug of choice for Virechana in Kushta. Samyak Virechana Lakshana was obtained. After Virechana Karma Samsarjana Krama has followed for Prakruti Prapta Purusha.

VII. Conclusion

The present case study showed that classical way of Virechana Karma with Manibhadra Churna is effective in Psoriasis. All the symptoms of psoriasis were totally reduced. Vyadhi Harana, Agni Vridhi, Laghutwa, Indriya Prasada and Twak Prasada were also obtained. No untoward effect was got during and after the treatment. After Samsarjana Karma, the patient has obtained his Prakruti.

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Review on Effect of Vitamin C on Immune System

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Abstract- Vitamin C is a water-soluble vitamin that is naturally present in some foods also available as dietary supplement. It's an essential vitamin, and so the body synthesizes vitamin c endogenously. Besides being involved in the biosynthesis of collagen, neurotransmitters, and protein metabolism, it is a potent antioxidant. Its role in immune-boosting is widely studied for various disease conditions. Vitamin c provide immune defense by supporting the innate and adaptive immune system. Vitamin c provides epithelial barrier function against pathogens and promotes the antioxidant activity of the skin, and thus protecting against environmental oxidative stress. Considering the immense organic, physiological capacities and remedial part of nutrient, this audit is an endeavor, to sum up confirmations in this unique circumstance. Understanding the various physiological pathways and effects of vitamin c is essential due to the ever-increasing number of infectious disease.

Keywords: *ascorbic acid, immune-modulatory, infection, oxidant, inflammation.*

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Review on Effect of Vitamin C on Immune System

Dr. Abel Abraham Thomas [α], Ms. Layana Roy [σ] & Ms. Fphamin. P. Philipose [ρ]

Abstract- Vitamin C is a water-soluble vitamin that is naturally present in some foods also available as dietary supplement. It's an essential vitamin, and so the body synthesizes vitamin c endogenously. Besides being involved in the biosynthesis of collagen, neurotransmitters, and protein metabolism, it is a potent antioxidant. Its role in immune-boosting is widely studied for various disease conditions. Vitamin c provide immune defense by supporting the innate and adaptive immune system. Vitamin c provides epithelial barrier function against pathogens and promotes the antioxidant activity of the skin, and thus protecting against environmental oxidative stress. Considering the immense organic, physiological capacities and remedial part of nutrient, this audit is an endeavor, to sum up confirmations in this unique circumstance. Understanding the various physiological pathways and effects of vitamin c is essential due to the ever-increasing number of infectious disease.

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I. Introduction

The immune system is a multifaceted network of specialized organs, tissues, cells, proteins, and chemicals, which protects the host from a range of pathogens, such as bacteria, viruses, fungi, and parasites . It is divided into epithelial barriers and cellular and humoral constituents of either innate or acquired immunity. More than half a century of research has shown vitamin C to be a crucial player in various aspects of the immune system [2]. Vitamin C is an essential nutrient that cannot be synthesized by humans due to the loss of an important enzyme in the biosynthetic pathway [3]. Severe vitamin C deficiency results in the potentially fatal disease scurvy. Scurvy is characterized by the weakening of collagenous structures, resulting in poor wound healing and impaired immunity. Individuals with scurvy are highly susceptible to potentially fatal infections such as pneumonia. In turn, infections can significantly impact vitamin C levels due to enhanced inflammation and metabolic requirements[1]

Vitamin C has several activities that could contribute to its immune-modulating effects. It is a highly effective antioxidant due to its ability to readily donate electrons, thus protecting bio molecules (proteins, lipids, carbohydrates, and nucleic acids) from damage by oxidants generated during normal cell metabolism and through exposure to toxins and pollutants [3]. Vitamin C is also a cofactor for a family of biosynthetic and gene regulatory monooxygenase and dioxygenase enzymes. Vitamin C is also a cofactor for the hydroxylase enzymes involved in the synthesis of catecholamine hormones, e.g., norepinephrine, andamidated peptide hormones, e.g. vasopressin, which are central to the cardiovascular response to severe infection. Vitamin C possesses antimicrobial properties, reducing the risk of infections [4], and has immunomodulatory functions, particularly in high concentrations [3]. However, one needs to take into consideration that inappropriate storage and preparation procedures of food might result in vitamin C degradation, further supporting the demand for appropriate dietary supplementation of this essential vitamin to reduce the risk of deficiency.

Furthermore, given that vitamin C is water-soluble, intoxication upon excess intake is virtually impossible since vitamin C concentrations exceeding the daily demands will be excrete via the kidneys[1]. Given its anti-infectious and immunomodulatory properties on one side and the lack of unwanted side effects on the other, vitamin C constitutes a promising antibiotic-independent strategy to combat and prevent bacterially(including enter pathogenic) infections[3]

II. Immunomodulatory Properties of Vitamin C

An optimum concentration of vitamin C is essential for a well-functional host defense mechanism. Several studies revealed that experimentally induced vitamin C deficiency reduces cellular and humoral immune responses. In clinical studies, vitamin C treatment in healthy subjects promoted and enhanced natural killer cell activities, lymphocyte proliferation, and chemotaxis. Furthermore, high doses of vitamin C stimulate murine immune cells, primarily dendritic cells, to more interleukin (IL)-12 secretions but also activated T and B cell functions [1]. Also, the observations that vitamin C concentrations in immune cells such as leukocytes are 10- to 100-fold higher than those measured in the plasma and the fact that these cells accumulate vitamin C against a concentration gradient further underline the immunological importance of vitamin C and support its role as a crucial player in

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various aspects of immune cell functions, such as immune cell proliferation and differentiation, besides its anti-inflammatory properties [2]. The newly characterized hydroxylase enzymes, which regulate the activity of the hypoxia-inducible factors (HIF), gene transcription, and cell signaling of immune cells, require vitamin C as a cofactor for optimal action. In the gastrointestinal tract, vitamin C plays a role as an essential micronutrient and antioxidant, protecting intestinal cells from inflammatory stimuli. However, in the inflamed mucosa of patients suffering from chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, the mucosal vitamin C concentrations are highly reduced. Also in a small study cohort intravenous high-dose vitamin C application was beneficial as an adjunct treatment option for colorectal cancer. Hence, vitamin C has shown to exhibit potent immunomodulatory activity in the course of distinct gastrointestinal inflammatory morbidities [3].

III. Role of Vitamin C in Barrier Integrity & Wound Healing

The skin has numerous essential functions, the primary of which is to act as a barrier against external agents, including pathogens. The epidermal layer is highly cellular, comprising primarily keratinocytes, while the dermal layer comprises fibroblasts, which secrete collagen fibers, the major component of the dermis. The skin contains millimolar concentrations of vitamin C, with higher levels found in the epidermis than the dermis [1]. Vitamin C is actively accumulated into the epidermal and dermal cells via the two sodium-dependent vitamin C transporter (SVCT) isoforms one and two, indicating that the vitamin has crucial functions within the skin...

Examples pointing on the role of vitamin C in the skin come from the symptoms of the vitamin C deficiency disease scurvy, which is characterized by bleeding gums, bruising, and impaired wound healing. These symptoms are thought to be a result of vitamin C as a co-factor for the prolyl and lysyl hydroxylase enzymes that stabilize the tertiary structure of collagen. Research has shown that vitamin C can also increase collagen gene expression in fibroblasts[3]. Vitamin C intervention studies in humans have pointed that enhanced vitamin C uptake into skin cells and enhanced oxidant scavenging activity of the skin. The elevated antioxidant status of the skin following vitamin C supplementation could protect against oxidative stress induced by environmental pollutants [2]. The antioxidant effects of vitamin C are likely to be enhanced in combination with vitamin E. Vitamin C supplementation of keratinocytes in culture increases differentiation and barrier function via modulating signaling and biosynthetic pathways, with resultant elevations in barrier lipid synthesis [4]

Dysfunctional epithelial barrier function in the lungs of animals with a serious infection can be restored by administration of vitamin C. It attribute to enhanced expression of tight junction proteins and the prevention of cyto skeletal rearrangements. Vitamin C appears to be particularly essential during wound healing, decreasing the expression of pro-inflammatory mediators and enhancing the expression of various wound healing mediators. Fibroblast cell culture experiments have also indicated that vitamin C can alter gene expression profiles within dermal fibroblasts, promoting fibroblast proliferation and migration, which is essential for tissue remodeling and wound healing. Following surgery, patients require relatively high intakes of vitamin C to normalize their plasma vitamin C status, and administration of antioxidant micronutrients, including vitamin C, to patients with disorders in wound healing, can shorten the time to wound closure. Leukocytes, mainly neutrophils and monocyte-derived macrophages, are main players in wound healing [3].

During the initial inflammatory stage, neutrophils migrate to the wound site to sterilize it via the release of reactive oxygen species (ROS) and antimicrobial proteins[2]. The neutrophils eventually undergo apoptosis and are cleared by macrophages, resulting in the resolution of the inflammatory response. However, in chronic, non-healing wounds, such as those observed in diabetics, the neutrophils persist and instead undergo necrotic cell death, which can perpetuate the inflammatory response and hinder wound healing. [3]

IV. Effect of Vitamin C on Distinct Immune Cells: Monocytes & Macrophages

The major component of the innate immune system, monocyte and macrophages are the first-line of defense against invading pathogens. The high vitamin C concentrations measured in monocytes underline the regulatory role of this vitamin in monocyte and macrophage functions.[3] An in vitro study revealed that intracellular accumulation of pharmacologic vitamin C concentrations could effectively inhibitapoptotic pathways in human monocytes. Vitamin C may also regulate distinct genes expressed in human macrophages, which are induced by lipopolysaccharide via nuclear factor kappa-light-chain-enhancer of activated B cells activation. Moreover, vitamin C application to monocytes derived from whole human blood diminished secretion of pro-inflammatory cytokines such as IL-6 and TNF- α [2]

a) Neutrophils

The exposure of neutrophils to oxidants inhibits their motility, which is related to oxidation of membrane lipids and affecting cell membrane fluidity. As a potent water-soluble antioxidant, vitamin C can neutralize

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reactive oxidants and regenerate cellular and membrane antioxidants such as glutathione and vitamin E (tocopherol)[3]. To protect themselves from oxidative damage, neutrophils accumulate vitamin C, resulting in improved cellular motility and migration in the response to chemotactic stimuli and, subsequently, in enhanced phagocytosis of microbes and generation of reactive oxygen species.

b) T Lymphocytes

T lymphocyte, as major players in acquired immunity, has impact by vitamin C. The development and maturation of murine and human T cells are enhanced in vitamin C in physiological concentrations, where the proliferation and viability of T lymphocytes are also affected. In human peripheral lymphocytes, vitamin C application promotes

T cell proliferation. However, a decreased number of human IL-2 producing T cells could be assessed in the presence of vitamin C. In contrast TNF-α and interferon (IFN)-γ expressing T lymphocytes were not affected. Inmurine splenic T cell cultures, only high vitamin C levels (0.25–0.5 mM) has shown to decrease T cell viability and secretion of anti-inflammatory cytokines such as TNF-α, IFN-γ, and IL-4 by activated T cells, which was not the case following incubation with lower vitamin C concentrations. Vitamin C administration during sepsis modify regulatory T cell activity by directly enhancing cell proliferation and by inhibiting the expression of distinct transcription factors, cytokines, and antigens directed against regulatory T Cells.[3]

c) B Lymphocytes

B lymphocytes are the main component of adaptive humoral immunity and control the antigen-specific immunoglobulin (Ig) production. Like T cells, B lymphocytes are capable of accumulating vitamin C, whereas, in the absence of vitamin C, the viability of B cells derived from murine spleens was shown to be decreased, further underlining the essential role of vitamin C in proliferation, viability, and function also of B cells

d) Natural Killer Cells

Natural killer (NK) cells are arising from the same lymphoid progenitors as T and B lymphocytes and play important roles in the elimination of pathogens, including viruses [2] . The proliferation of human NK cells derived from peripheral blood mononuclear cells can be accelerated by co-incubation with vitamin C resulting in higher cell numbers with accurate functional capacity.

Furthermore, the cytotoxic capabilities of NK cells can block via platelet aggregation around migrating tumor cells, whereas in vitro vitamin C application increased the cytotoxic activity of NK cells directed against tumor cells. Patients suffering from β-thalassemia major are known to display compromised cytotoxic activity of NK cells, which could be rescued by vitamin C application [3].

V. The Role of Ascorbate in the Hypoxic Response & Implications for Immune Cell Function

The hydroxylase enzymes that regulate the activity of the hypoxia-inducible factors (HIF)s require ascorbate for optimal action. The HIFs are controlled by hydroxylation of proline and asparagine residues on the regulatory alpha subunit and, in response to changes in oxygen availability, direct the transcription of hundreds of genes via the hypoxia response element [1]. The dependence of the hydroxylases on ascorbate as a cofactor has been demonstrated in cell-free systems, with other reducing agents such as glutathione being very much less effective as a recycler of the hydroxylase active site. Depleted intracellular ascorbate levels have been shown to contribute to the up-regulation of HIF activation, particularly under conditions of mild or moderate hypoxia. The interaction between ascorbate and the HIFs is relevant to the function of immune cells in both inflammation and cancer. Inflammatory sites are known to be under hypoxic stress, potentially due to the increased oxidative metabolism of inflammatory cells. Growing tumors are also well characterized as being hypoxic tissues due to rapid proliferation and outgrowth of the established blood supply [2]. The resulting up-regulation of the HIFs is the main reason for the activation of glycolysis, angiogenesis, resistance to chemotherapy, and the promotion of a stem cell phenotype, thereby promoting tumor growth and metastasis. At inflammatory sites and in tumor tissue, the hypoxic environment affects immune cell function and, given the interdependence between the HIFs and cellular ascorbate [3].

VI. Antimicrobial Properties Of Vitamin C

Vitamin C is known for its antimicrobial effects directed against Mycobacterium tuberculosis, the infectious agent of human tuberculosis. An in vivo study revealed that administration of tuberculosis sputum to vitamin C-deficient guinea pigs led to intestinal tuberculosis. In contrast, the guinea pigs that had received vitamin C-containing tomato juice did not suffer from the disease [1]. Initially, it was hypothesized that the antimicrobial properties of vitamin C were due to its pH lowering effect. Another study, however, could prove potent antimicrobial effects of vitamin C directed against group a hemolytic streptococci, even in a nearly pH-neutral environment. Further studies assessed the antibacterial effects of vitamin C against distinct bacterial (opportunistic) pathogens in more detail, applying microdilution assays [1]. Vitamin C

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concentrations of 0.31 mg/mL could effectively inhibit Pseudomonas aeruginosa growth in vitro. Also, vitamin C application at low concentration (0.15 mg/ml) to inhibit the growth of Staphylococcus aureus. The antibacterial effects of vitamin C might be both bacterial strain and concentration dependent.

VII. Review of Studies Conducted

Anitra. C. C. and Silvia. M did a review on the topic "Vitamin C and Immune function." They point out that vitamin C appears to exert a multitude of beneficial effects on cellular functions of both the innate and adaptive immune system. Even though vitamin C have potent antioxidant activity in the body against both endogenous and exogenous oxidative reactions, likely its action as a cofactor for numerous biosynthetic and generegulatory enzymes plays a critical role in its immune - modulating effects. Vitamin C stimulates neutrophil migration to the infection site, enhances phagocytosis and oxidant generation, and microbial killing. At the same time, it protects host tissue from excessive damage by increasing neutrophil apoptosis and clearance by macrophages, and decreasing neutrophil necrosis. Thus, it is apparent that vitamin C is necessary for the immune system to mount and sustain an adequate response against pathogens, while avoiding further damage to the host. Vitamin C helps in preventing and treating respiratory and systemic infections by various immune cell functions alterations. Prophylactic prevention of malday requires dietary vitamin C intakes that provide at least adequate, if not saturating plasma levels, which optimize cell and tissue levels

Abel. A, Juliet. P. M, Margaret. C.J and Margreet. C.D did a review on the topic "Vitamin C and immune cell function in inflammation and cancer." They explain that Vitamin C (ascorbate) when maintained at peak levels in most immune cells and can alter many aspects of the immune response. At Intracellular levels generally it responds to variations in plasma ascorbate availability and imbalance during severe stress can result in low plasma ascorbic acid status. Intracellular ascorbate is essential, in particular, acts as an enzyme cofactor for Fe- or Cu-containing oxygenases. The demonstrated dependency of the Fe-containing 2-oxoglutarate-dependent di oxygenase family on ascorbate availability and the involvement of members of this family of enzymes on many immune cell functions provide a rational basis for the belief that ascorbate supports the immune system. Ascorbate availability will influence HIF activation and immune cell function in hypoxic inflammatory and tumor environments, affecting the resolution of inflammation..

Soraya. M, Stefan. B and Markus. H.M studied the topic" Immune modulatory and antimicrobial effects of Vitamin C." The biological role of vitamin C is related to its reversibly oxidized form and is involved in a multitude of both enzymatic and non-enzymatic processes. Additionally, vitamin C is a powerful antioxidant compound directed against free radicals and ROS. Leukocytes , including lymphocytes , can actively accumulate vitamin C against a concentration gradient, which underlines not only vitamin C dependent functional but also developmental immune cell features. Vitamin C has a good impact on both innate and adaptive immune responses. Vitamin C is also involved in bacterial metabolism. It is proven that several bacteria can ferment vitamin C, whereas the presence of this vitamin exposes others to oxidative stress, which may result in bacterial growth inhibition. The potent antibacterial effects of vitamin C are due to its low pH where bacterial growth is inhibited. Notably, vitamin C can inhibit the growth of S. aureus and streptococci even under neutral Ph conditions. Potent growth-inhibitory 245 effects against multi-drug resistant (MDR) bacteria such as MRSA and proven synergistic effects with natural or synthetic antibiotic compounds.

Benjamin. S.V did a study on the topic "Vitamin C and the immune response in health and disease." Vitamin C can affect various aspects of the immune process. Its concentration in leukocytes and rapid utilization during infection, and its depression in clinical situations associated with reduced immunologic function have suggested a role for the vitamin in the immune response.

Ascorbic acid affect other facets of the immune response, including delayed hypersensitivity and monocyte-macrophage reactivity. The introduction of ascorbic acid as an antiviral and antibacterial agent needs further stimulated study on the possible immunologic mechanisms involved in its protective role. Vitamin C has also been used to treat several 254 immunology associated blood disorders, including rheumatic and allergic diseases. In patients with neutrophilic dysfunctions such as Chediak-Higashi syndrome, chronic granulomatous disease, and recurrent infections, vitamin C has been administered and shows some immunologic and clinical benefit.

Nilashi M, Samad S,Shahmoadi I, Ahmadi Hossein, Akbari Elnaz, Rashid T A did a study on "The COVID-19 infection and the immune system: The role of complementary and alternative medicines". The study was conducted at Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City, Vietnam, School of Engineering, University of California, Merced, USA, Health Information Management Department, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran. This study investigates the efficacy of Complementary and Alternative Medicines (CAMs) in boosting immune response against COVID-19. As per the study due to the wide spread universal impact of the COVID -19 and as there is no clinically

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approved antiviral introduction or vaccination exits it is critical to analyze the nature of the disease and relation with human immune system and to develop immunity boosting measures against COVID-19. Recognizing the disease and its consequences on the immune system will support its better management providing preferred treatment strategies and more effective prevention. It is found that CAMs are effective in boosting immune response and diseases. Several cases of CAMs proposed for prohibiting and curing diseases are identified. An example for CAM is CURCUMIN which is found to improve the immune function against many disease conditions. It acts by modulating the response of T cells. It has been demonstrated that Vitamin C, Vitamin D and zinc boost the immune system versus viruses. It is guaranteed that the Covid pandemic can be fundamentally brought down by utilization of high use of vitamin C. Antiviral action of nutrient C has been perceived and affirmed in the past, however it's generally less communicated and specifically, there exist lack of data on its impact on Covid. Vitamin C can be directed with expected meds to treat the malady in intense conditions. Early administration of vitamin C as IV is found to be effective in the treatment of COVID-19.

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Bendich A did a study on "Physiological Role of Antioxidants in the Immune System." According to this in order to tackle the large number of free radicals that generates in our body, it is critical eradicating them with antioxidants. There is much strong evidence that suggests that supplementation with vitamins A, C provides a safe and effective means to enhance immune functions. Vitamin A supplementation significantly effective in measles in children.

The protective effects of vitamin c were associated with an enhancement in immune responses and reduced the rate of secondary infections. Supplementation with vitamin C is co-related with the enhancement of immune responses in several population groups. Many of the immune response modulations destroys cancer cells. The antioxidant micronutrients protected immune responses from the immunosuppressive effects. Thus, antioxidant vitamins enhance immune responses that are involved in protection from infection and malignancies.

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The data strongly suggest that the intake is needed to improve immune responses.

VIII. Discussion

Vitamin c has many beneficial effects on cellular function of the innate and adaptive immune system. Vitamin c is a potent antioxidant give protection against endogenous and exogenous oxidative reactions, it act as a cofactor for numerous biosynthetic and gene regulatory process and plays a crucial role in its immune-modulation. Vitamin C activate neutrophil migration to the infection site, improve phagocytosis and provide antimicrobial activity. Vitamin c can be used to and treat respiratory and foundational contaminations by improving different resistant cell capacities. Prophylactic counteraction of contamination requires dietary nutrient c admissions that give at any rate sufficient, if not soaking plasma levels (i.e., 100–200 mg/day), which upgrade cell and tissue levels. Conversely, treatment of set up diseases requires essentially higher (gram) portions of the nutrient to make up for the expanded metabolic interest. Vitamin c has a number of activities that could contribute to its immune-modulating effects. It is a highly effective antioxidant, due to its ability to readily donate electrons, thus protecting important bio molecules (proteins, lipids, carbohydrates, and nucleic acids) from damage by oxidants generated during normal cell metabolism and through exposure to toxins and pollutants

IX. Conclusion

In clinical studies, vitamin c treatment in healthy subjects promoted and enhanced natural killer cell activities, lymphocyte proliferation, and chemotaxis. Furthermore, high doses of vitamin c not only stimulate murine immune cells, primarily dendritic cells, to more distinct interleukin-12 secretion, but also activated T and B cell functions. Overall there is large body of evidence supporting that maintaining healthy vitamin c level can have a protective function against age related cognitive decline but avoiding vitamin c deficiency is likely to be more beneficial than taking supplements on top of normal healthy diet. Study on the topic “immuno modulatory and antimicrobial effects of vitamin c” conducted by M.soraya, B.stefan and H.M.markus explains well about the biological pathway of vitamin c. Thus, it is apparent that vitamin c is necessary for the immune system to mount and sustain an adequate response against pathogens, whilst avoiding excessive damage to the host.

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Abbreviations

CFU: colony-forming units
DHA: dehydroascorbic acid
HIF: hypoxia-inducible factors
IBD: inflammatory bowel disease
IFN: interferon
Ig: immunoglobulin
IL: interleukin
LPS: lipopolysaccharide
MDR: multi-drug resistant
MRSA: methicillin-resistant Staphylococcus aureus
NK cell: natural killer cell
ROS: reactive oxygen species
SPF: specific pathogen-free
SVCT: sodium-dependent vitamin C transporter
TNF: tumor necrosis factor

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Leading Role of the Principles of Interaction between the Natural Physical Factors and Integral Organism in Medicine of the Future

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Abstract- The paper discusses the search of evidences of advantage of the physiotherapy over the drug therapy by the parameters and treatment methods according to clinical stage of a disease development, based on the results of labor medical examination and improvement of the quality of life.

The above indicators were confirmed with a high statistical accuracy by example of a new rehabilitation technology: "Underwater horizontal spine traction with underwater phototherapy to solve an essential medical and social problem: treatment of patients with degenerative and dystrophic lesions of the lumbosacral spine with herniated protrusions of intervertebral discs, being one of the most common neurological pathologies worldwide.

Keywords: physiodynamics, physiokinetics, supramolecular structures, blood spectrum biopsy.

GJMR-B Classification: NLMC Code: QV 4

LEADINGROLEPRINCIPLESINTERACTIONBETWEENNATURALPHYSICALFACTORSINTEGRALORGANISMMEDICINEFUTURE

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Leading Role of the Principles of Interaction between the Natural Physical Factors and Integral Organism in Medicine of the Future

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Abstract- The paper discusses the search of evidences of advantage of the physiotherapy over the drug therapy by the parameters and treatment methods according to clinical stage of a disease development, based on the results of labor medical examination and improvement of the quality of life.

The above indicators were confirmed with a high statistical accuracy by example of a new rehabilitation technology: "Underwater horizontal spine traction with underwater phototherapy to solve an essential medical and social problem: treatment of patients with degenerative and dystrophic lesions of the lumbosacral spine with herniated protrusions of intervertebral discs, being one of the most common neurological pathologies worldwide.

Based on the achievements in physics, i.e. discovery of "evanescent waves", "scanning tunneling microscope"; "AC and DC Josephson effects", development of highly sensitive equipment and discovery by the author of the present article of a highly informative, non-invasive, simple, harmless method of studying the mechanism of action of physical factors on the integral organism from any part of the skin surface, i.e. "blood spectrum biopsy" displaying the complete information picture of an organism, it became possible to create a new theory of a mechanism of action of physical factors on the supramolecular level of the integral organism on the principle of "tunnel effect".

Keywords: physiodynamics, physiokinetics, supramolecular structures, blood spectrum biopsy.

I. Introduction

Any pharmacological preparation, from the moment of its introduction into organism and during the whole way of movement is exposed to complex physical and chemical changes with formation of reversible and irreversible compounds (intermediate formations) with obligatory release of a certain energy for continuation of cyclic process of transition from one state to the next one up to exit from the integral organism.

It is known that "the interaction of a medicinal product with the organism is studied in two aspects: how it affects the body (pharmacodynamics) and what happens to it in the body (pharmacokinetics). Pharmacodynamics studies localization, mechanism of action and pharmacological effects of the medicinal substances.

Pharmacokinetics studies the common factors of absorption, distribution and elimination of the medicinal substances in a human or animal organism. [1]

Herewith, it should be noted that the speed, scale, content and time of emergence of intermediate formations of pharmacological preparation in the organism are strictly individual for each patient.

The pharmacodynamics and pharmacokinetics of all medicinal products interacting with the body should be studied using quick, harmless and highly informative methods, before such products are accepted for medical use.

Compliance with this concept contributes to ensuring high therapeutic effect, primary and secondary prevention of diseases, prevention of complications and side effects on the body. This is not observed in global healthcare and pharmaceutical practice due to the lack of methods of research of pharmacological preparations at the supramolecular level.

From the organism's viewpoint, any substance coming from outside is regarded as a foreign body, thereby initiating a system of quick escape of the same. Even an own blood outside the vascular bed is treated as a foreign body by the organism. Therefore, an immediate shift of work of all organs and systems of the body into extraordinary mode takes place.

It should be noted, given the present state of development of the medicine, that there are no methods to determine the cycle temporal level of each system at the moment of effect of the medicinal substance on organism, in its transitional states at the supramolecular level and when all systems return to normal mode of life.

In this regard, it is difficult to imagine the advantage of a particular medicinal substance in general and, in particular, for a specific patient. The lack of data in the chronological sequence of the medicinal substance in its path to achieving the goal calls into question the prevalence of the drug therapy over physiotherapy.

It is known that the final characteristic of any medicinal substance at the supramolecular level is an "energy", which is difficult to dose and regulate for therapeutic purposes - this is the reason for the lack of

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these characteristics in the global medical and pharmaceutical literature.

The impact of energy of any physical factor is dosed and regulated (physiodynamics) with the help of nanotechnologies and its path to each molecule of the integral organism (physiokinetics) is easily traced without disturbing supramolecular structures and any negative consequences.

The modern global pharmaceutical science does not have such a high level of control over the path of a medicinal substance in the body.

According to A.L. Chizhevsky "an obligatory condition for the life of a living organism is an exchange of the "electrical" component being the foundation of metabolism process, and the total energy content in the cellular structures of the body has a strictly defined meaning". [2]

Bioelectric potential for each human being is strictly individual both in norm and pathology. In this regard, any nosology causes in each individual a deviation of his or her bioelectric potential in accordance with the stage of disease development, i.e. development of intermediate states of the body with certain disorders of its supramolecular structures.

This, in turn, determines the clinical findings at the time of examination of the patient and constitutes the leading condition for selecting the right treatment strategy for any specialist physician, so that the regression of the disease is accompanied by the restoration of destroyed supramolecular structures, avoiding new gross disturbances at any level of the integral organism.

This concept is not the main principle for drug therapy due to the lack of highly informative research methods: frequency, dose, mechanism of action of pharmacological preparations at the supramolecular level.

II. Research Materials & Methods

a) Experimental studies

Methods of experimental study of the action of PVIP light device "BIOPTRON" via fiber optic cable to water, blood plasma and integral organism: IR spectroscopy in the region 4000-400 cm^{-1} on a Fourier spectrometer Perkin-Elmer 2000 between the plates KRS-5, conducted at the Establishment of the Academy of Science A.A. Frumkin Institute of Physical Chemistry and Electrochemistry of the Russian Academy of Science (IPCE of RAS), Moscow; Experimental measurements of the spectra of Raman scattering (Raman effect) of various water samples on the automated fiber optic spectrometers at the Institute of Spectroscopy of the Russian Academy of Sciences RAS (ISAS), town Troitsk, Moscow region and the Research Center of fiber optics of the Russian Academy of Sciences, Moscow; Evanescent infrared spectroscopy of the skin in vivo by fiber optic sensor, at the Scientific center of Fiber Optics of the Russian Academy of Sciences, Moscow.

b) Clinical trials

This paper is based on analysis of the treatment outcomes of 745 individuals (454 males and 291 females) aged 17 to 60 years with degenerative and dystrophic processes of intervebral discs of lumbosacral spine, with hernial protrusions into the spinal canal of up to 13 mm.

In accordance with the purpose and tasks of the trial, all patients were examined and splitted up into groups according to following indices: four age subgroups: 1) aged 17 to 30 years; 2) 31 to 40 years; 3) 41 to 50 years; 4) 51 to 60 years) and by gender (males and females); by duration of the disease (n=745): 1) 1 to 5 years; 2) 6 to 10 years; 3) more than 10 years; by incidence of various clinical evidences of degenerative and dystrophic processes in lumbosacral spine (n=745); by quantitative characteristic of radiodiagnostic data: computer tomography (CT) – 244, magnetic resonance imaging (MRI) – 269, X-ray radiography – 745; by MRI results and age groups of randomized trial population n=269 with hernial protrusion into the spinal canal L4-S1 of up to 5 mm and from 5 to 13 mm; All of the patients were splitted up into 5 groups by treatment methods and into 4 groups by age.

1st control group – 175 patients: 24 patients aged 17 to 30 years, 37 patients aged 31 to 40 years, 65 patients aged 41 to 50 years, 49 patients aged 51 to 60 years, were administered the drug therapy according to Moscow standard. Agerage therapy regimen was 20 days.

2nd control group – 157 patients: 26 patients aged 17 to 30 years, 39 patients aged 31 to 40 years, 62 patients aged 41 to 50 years, 30 patients aged 51 to 60 years were administered the physiotherapy (magnetotherapy, amplipulse therapy, laser therapy, acupuncture, ultrasonic therapy, therapeutic physical training in various combinations) with drug therapy.

Average therapy regimen was 17 days. Information for each patient was collected according to medical documents (outpatient records, medical and physiotherapeutic treatment procedural records), registers of primary and recurrent patients, registers of specialists), as well as by interviews and questionnaires according to the "map of examination for detection of musculoskeletal pathology" (Appendix 1) developed by us, which represents a slightly modified standard WHO questionnaire.

The rest of 413 patients under attendance were distributed into three groups by the adopted treatment methods and into four age groups, the same as two control groups:

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3rd group: 26 patients aged 17 to 30 years, 39 patients aged 31 to 40 years, 55 patients aged 41 to 50 years, 33 patients aged 51 to 60 years, a total of 153 patients were administered the physiotherapy with underwater phototherapy with the average treatment regimen of 16 days.

4th group: 26 patients aged 17 to 30 years, 32 patients aged 31 to 40 years, 43 patients aged 41 to 50 years, 31 patients aged 51 to 60 years, a total of 132 patients were administered the physiotherapy with underwater spine traction. Average treatment regimen was 15 days.

5th group: 30 patients aged 17 to 30 years, 30 patients aged 31 to 40 years, 45 patients aged 41 to 50 years, 23 patients aged 51 to 60 years, a total of 128 patients were administered the underwater spine traction with underwater phototherapy. Average treatment regimen was 16 days.

c) Results of the trial and discussion

Clinical physiotherapy is closely connected with the other fields of the medicine, physics and biology.

Thus, the investigation of etiology and pathogenesis of many diseases allows not only the application of the necessary physical factor, but the development of a rational method, its application, combination with other physical factors as well [3,4,5,6].

The achievements in physics and development of highly sensitive equipment made possible determination of the mechanism of action of low-energy physical factors on cellular and subcellular levels of the organism [7,8,9].

It is established that when any electromagnetic wave passes through the fiber, evanescent waves are always formed around the fiber perpendicular to the outer surface of the latter and they attenuate at a distance from it.

These previously unknown light properties were recently discovered by scientists from Japan, USA, Ukraine and Korea [10].

In this regard, we have conducted a number of experimental studies (recording of standing evanescent wave photons on the skin surface after exposure to PVIP (Polychromatic Visible and Infrared Polarized) light of 480-3400 nm).

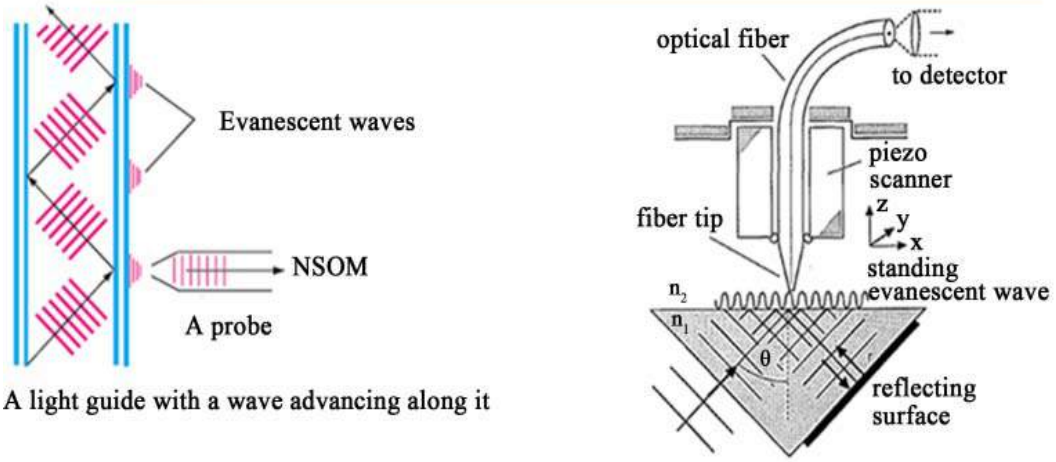


Diagram of measuring the state of a light wave advancing along the light guide. Damping evanescent waves exist near the light guide's surface (this, in fact, is the near field area). By using the NSOM probe it is possible to transform a small amount of photons from the near field into the measured signal.

Diagram of registering photons of a standing evanescent wave bonded with top prism surface using a scanning tunneling photon microscope.

Fig. 1: Evanescent waves.

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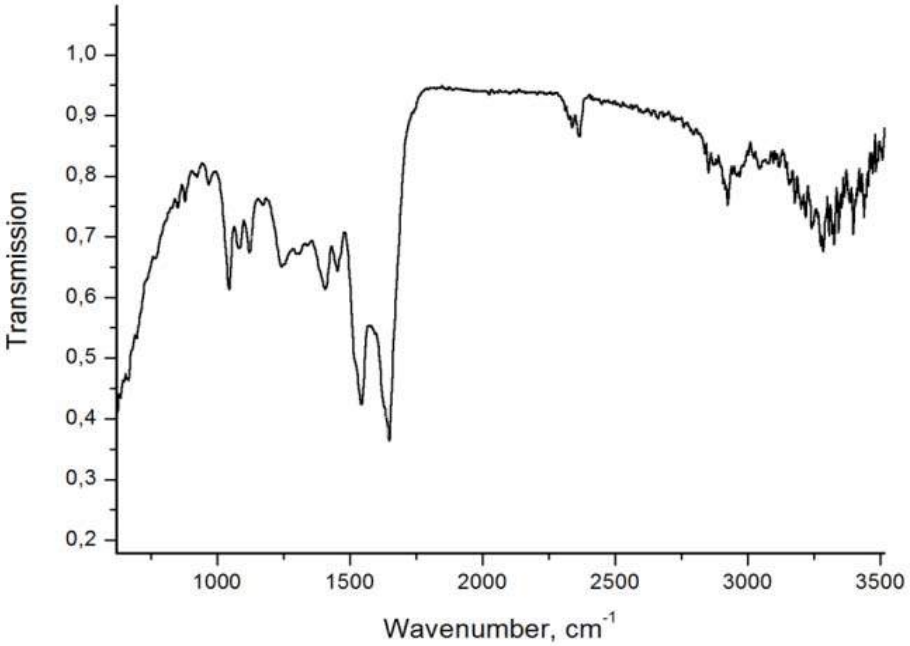


Fig. 2: IR spectrum of the skin after hand exposure to yellow light through the optic fiber cable during ten minutes.

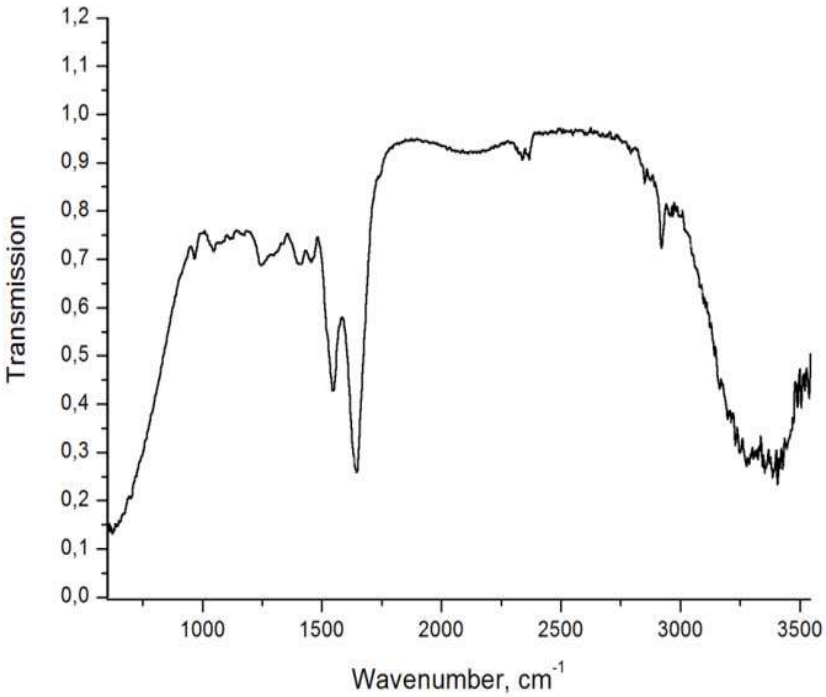


Fig. 3: IR spectrum of the skin after hand immersion into the water irradiated by yellow light through the optic fiber cable during ten minutes.

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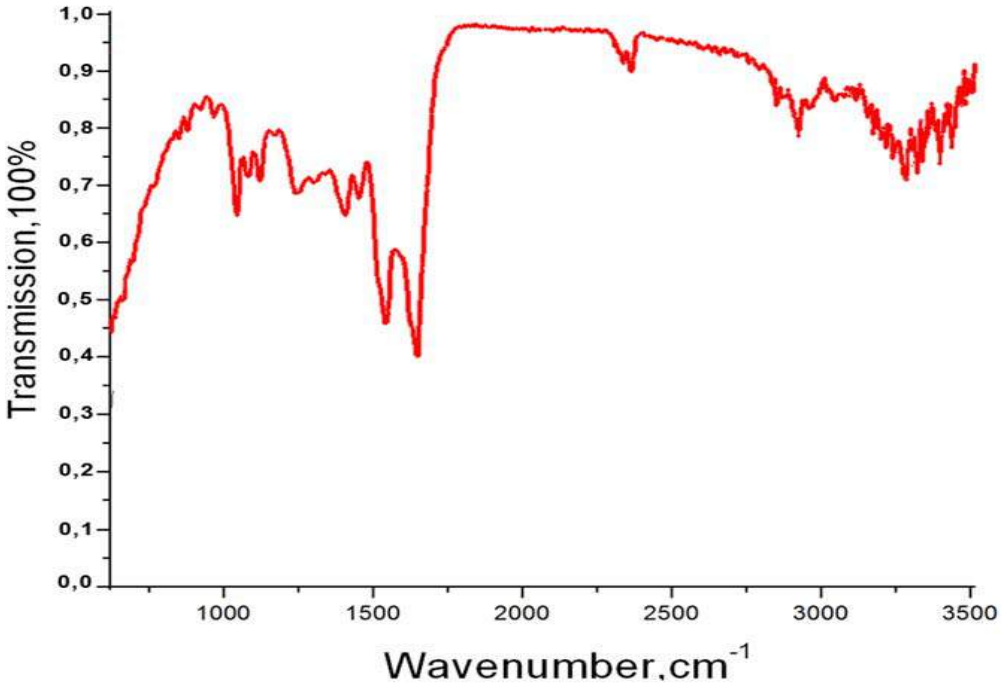


Fig. 4: IR spectrum of the skin after hand exposure to polarized light emitted by Bioptron apparatus during 10 minutes.

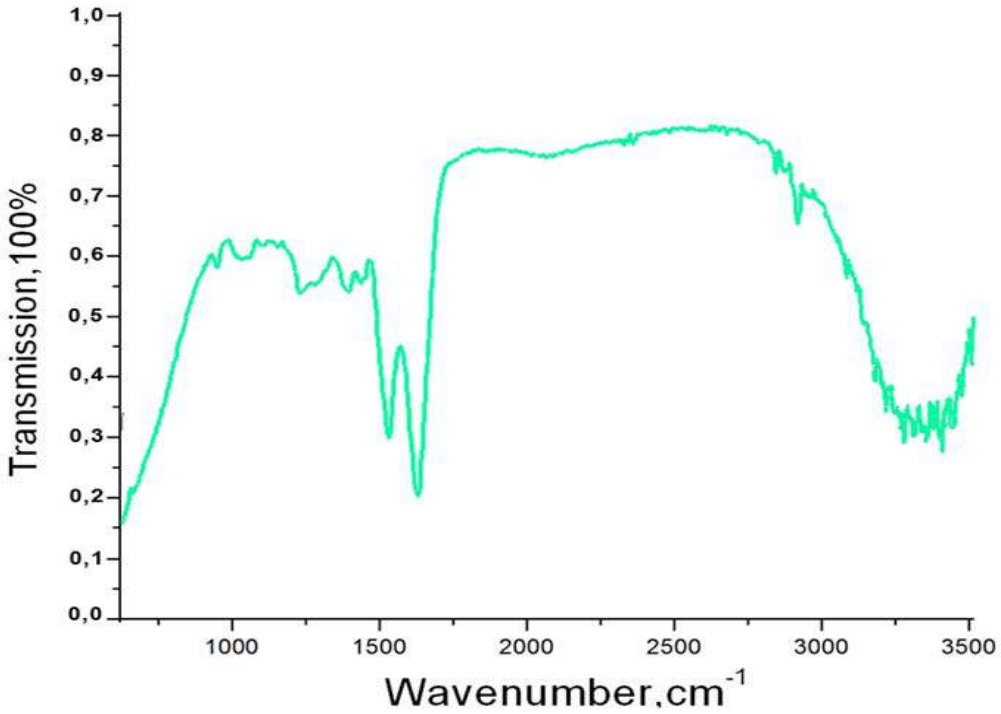


Fig. 5: IR spectrum of the skin after hand immersion into the water irradiated by Bioptron emitted light during 10 minutes.

It was established that the evanescent infrared spectra of the skin after exposure to water activated by light through the fiber optic cable from Bioptron device demonstrate an increase in the absorption area within the wavelength ranges from 3200 to 3500 cm^{-1} and within the range up to 800 cm^{-1}, i.e. there is an increase in hydration [11,12,13,14].

In this regard, there is a substantiation to use phototherapy with Bioptron device through fiber optic cable both under direct exposure and indirectly, i.e.

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through water, for treatment of various diseases of the musculoskeletal system, skin and other organs and systems.

Based on the above experiments, it is possible to conclude that the photo excitation of water by Bioptron source indeed results in changes of water structure. This was made possible by absorbing the radiation from the source in the water, stimulating the growth of water nanoclusters linked by hydrogen bond, which, in its turn, was made possible by discovering the unusual properties of light by the abovementioned scientists (emergence of evanescent waves) and creation of "scanning tunneling microscope". (Dr. Stephen Mendak and his colleagues from Germany created a working tool able to reconstruct two-dimensional images of three-dimensional nanoscale objects using the light of visible frequency and the near infrared spectrum. The device was developed on the basis of the "super lenses" made of thin silver strips in the form of a tube with center opening of about 2 μm. The evanescent waves pass from its inner surface perpendicularly to the circumference and during such movement there is a primary image magnification, i.e. the “scanning tunneling microscope”) [10]

Russian scientist, winner of the Lenin Prize in physics Gurgen Ashotovich Askarian in 1982 experimentally proved: "increasing in the passage of laser and other radiation through soft turbid physical and biological environments" [15].

It is known that one of the interesting applications of laser is based on its stimulating effect on regenerative, anti-inflammatory and immune processes in cells and tissues of the body, especially in view of the resonant nature of absorption and stimulation (one of the absorption fields is close to the generation line of a He-Ne- laser with a wavelength of 0.63 μm).

It is precisely these processes that link the use of such lasers with the treatment of purulent processes of the maxillary sinuses, trophic ulcers, non-healing wounds, stomatitis, polyneuritis and other pathological processes.

In this regard, we widely used low-energy lasers in the comprehensive therapy of trophic long-term non-healing wounds, on an annual basis, for 150-170 patients in average, according to the following method:

Magneto therapy of a limb during 5-7 minutes up to 30 mt, transversely to the wound area during 5-7 minutes up to 30 mt (Polyus-1 device); ultratone therapy (supersonic frequency currents) on the wound area, average power, during 10 minutes; laser therapy: 4 areas around the wound perimeter, stably for 4 minutes each, 1500 Hz and in the fifth area in the wound center, stably for 4 minutes, 80 Hz.

The treatment regimen consisted of 17 procedures.

There was always a persistent remission and complete healing of the wound.

Over the past five years, an average of 180 patients with the diagnosis of "bilateral purulent process of the maxillary sinuses" were treated annually by physiotherapy according to the following profile:

UHF, maxillary sinus area 40 W, 10 minutes, treatment regimen of 10 days;

irradiation of nasal passages with short-wave ultraviolet rays for 40 seconds, 10 days;

laser therapy, area of the maxillary sinuses with moderate pressure of the device Uzor-A-2K emitters of soft tissues over the areas of the nasal sinuses, 5 Hz, for 5 minutes, treatment regimen of 10 days.

There was always a clinical recovery under the X-ray radiography monitoring of the paranasal sinuses and patients did not need surgical treatment.

G. A. Askaryan used in his first experiment a layer of polyurethane foam simulating a highly scattering medium. He used as an experiment a continuously operating He-Ne laser LG-75 with a power of 15-20 mW. Its beam was aimed at the test layer contained by a cylinder or tube. A spot of the scattered light was recorded by the camera at the exit from the scattering layer. The spot of scattering light at the exit depended on thickness of the compressed layer. The lower the thickness of the compressed layer was, the larger was the spot of the scattered light at the exit [15].

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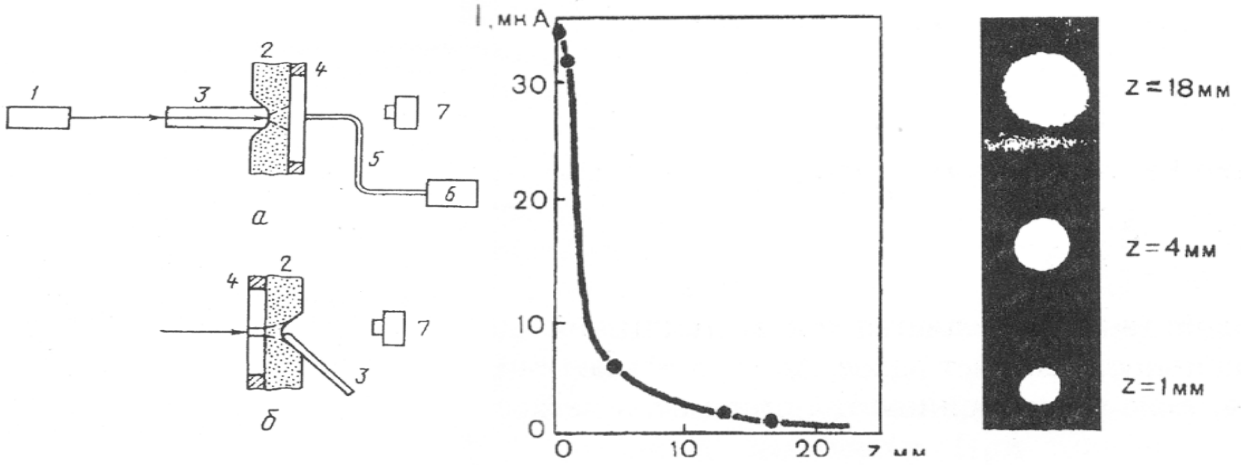


Fig. 6: Increased light penetration when pressing on the foam layer

In his second experiment, G. A. Askarian investigated the change in the light penetration through tissues of the human body. He used a palm as a scattering layer, the center of which was hit by a helium-neon laser beam. The thickness of the palm in its central part was 2.7 cm and 2 cm with slight pain compression.

When the beam hit the back of the right palm and when the glass stick pressed on the flesh of the palm from the opposite side, a sharp increase in the light passage was observed. When pressing the left palm on the plexiglass cylinder through which the light passed, the increased light passage observed from the opposite side. Such increase was observed already when compressing from 2.7 to 2 cm, i.e. the translucence effect is much more intense when pressing the palm than when using the foam [15].

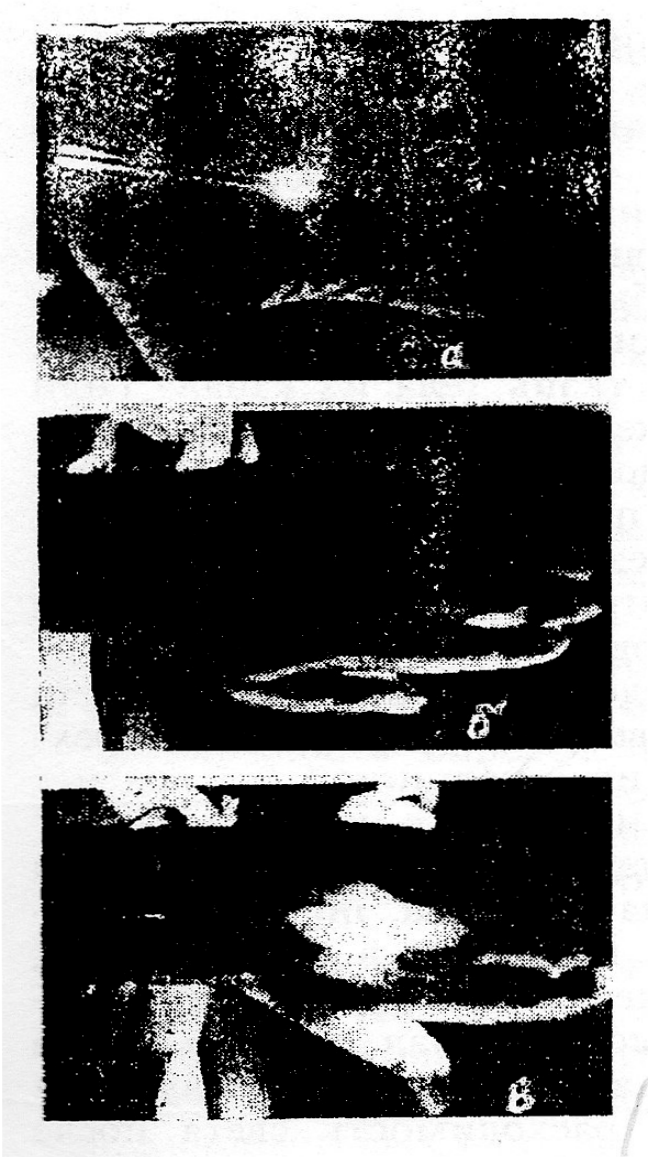


Fig. 7: Increased light penetration when pressing on the biologic body layer

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The author attributes this to the lateral displacement of blood and tissue. However, it should be noted in his experiment that even the thicker parts of the palm, i.e. the flesh with blood and area at the phalanges of fingers are more permeable to light and more susceptible to translucence by compression than its central part. It is interesting to note the relaxation of translucence: when the pressure is released, the translucence does not disappear immediately – the trace of pressure passes the light for another 1 to 3 seconds. This is confirmed in papers [11,12] - irradiation after effect.

The works [12,13,14,16] established that the cardiovascular, nervous and lymphatic systems can be the light guides and evanescent (attenuating) waves also form around them, perpendicular to the outer surface of vessels, capillaries, and nerve roots, when they are exposed to electromagnetic waves in any areas of the skin surface.

In this regard, we have developed a sensor-mininano microscope, through which a direct and back communication of internal organs and systems of the integral organism is carried out.

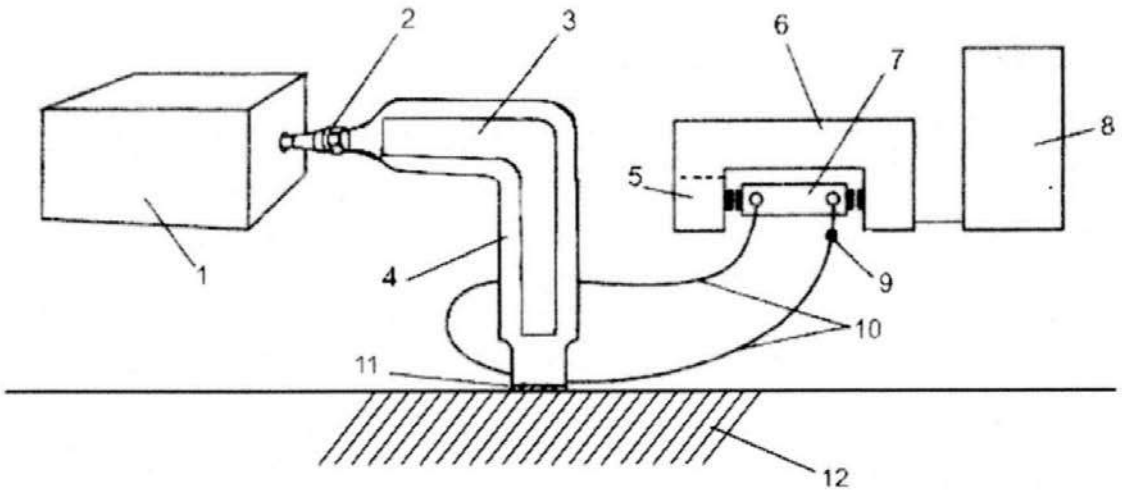


Fig. 8: Recording of direct and back communication of all organs and systems of the integral organism from the skin surface.

1. Light source.
2. Coupling head inserted into the opening of the metal box (connects the source of light and optical fiber cable).
3. Optical fiber cable.
4. Device of information exchange between the integral organism and biosphere.

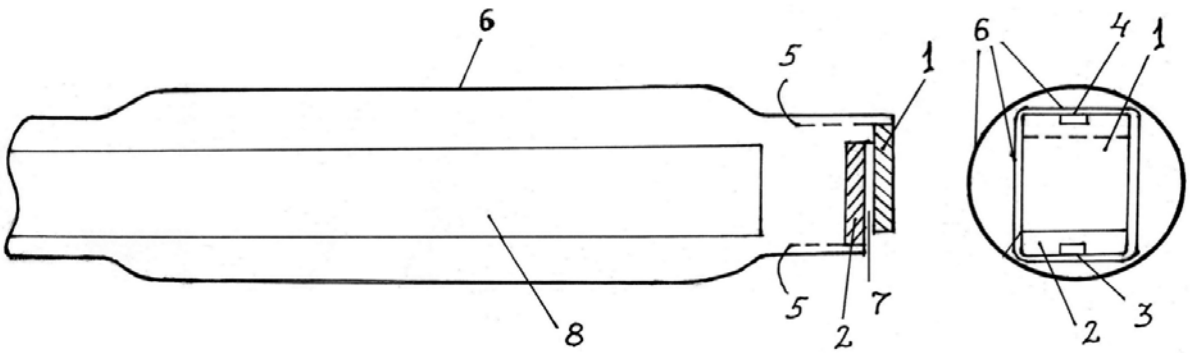


Fig. 8(4)

1. *Upper glass plate.*
2. *Lower glass plate.*
3. *Silver plate.*
4. *Silver plate.*
5. *Terminals.*
6. *Flexible non-metallic tube.*
7. *The space between the skin surface of the skin of a living organism and the upper glass plate with a transition to the space between two glass plates.*
8. *Optical fiber cable.*
5. DTGS pyroelectric detector
6. Spectrometer Bruker «Vector 22».

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7. The mirror-lens accessory for connection of "Device of information exchange between the integral organism and biosphere" to Fourier-transform spectrometer "Vector 22".
8. Computer.
9. Contact switch.
10. Terminals from the shell-less fiber AgClBr.
11. Sensor-mininanomicroscope.
12. Skin surface of the integral organism.

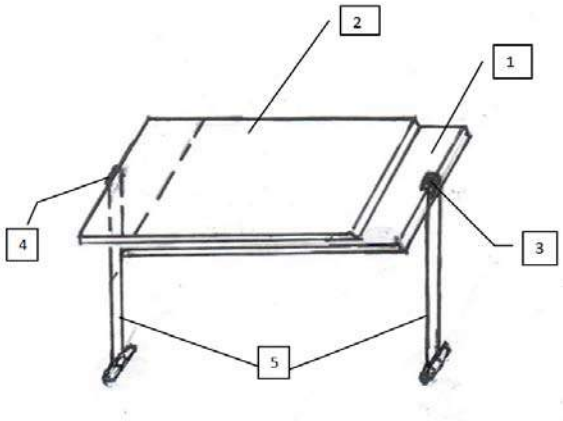


Fig. 8(11)

1. *Upper glass plate.*
2. *Lower glass plate.*
3. *Silver contact plate.*
4. *Silver contact plate.*
5. *Terminals from the silver plates.*

The mininano microscope sensor is made of two glass plates, placed one above each other with displacement of 5 mm, as to provide space between the skin epidermis and upper glass plate, as well as of 7 μm space between the glass plates for information reciprocal exchange between the integral organism and biosphere through the perspiration system and optical fiber cable.

Therefore, evanescent IR spectroscopy of the attenuated total reflection when touching the IR fiber us an unique, non-damaging, not requiring special preparation of the skin method - "Blood Spectrum Biopsy", which reflects the entire information picture of the body at the supramolecular (atomic) level (Fig. 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13,)

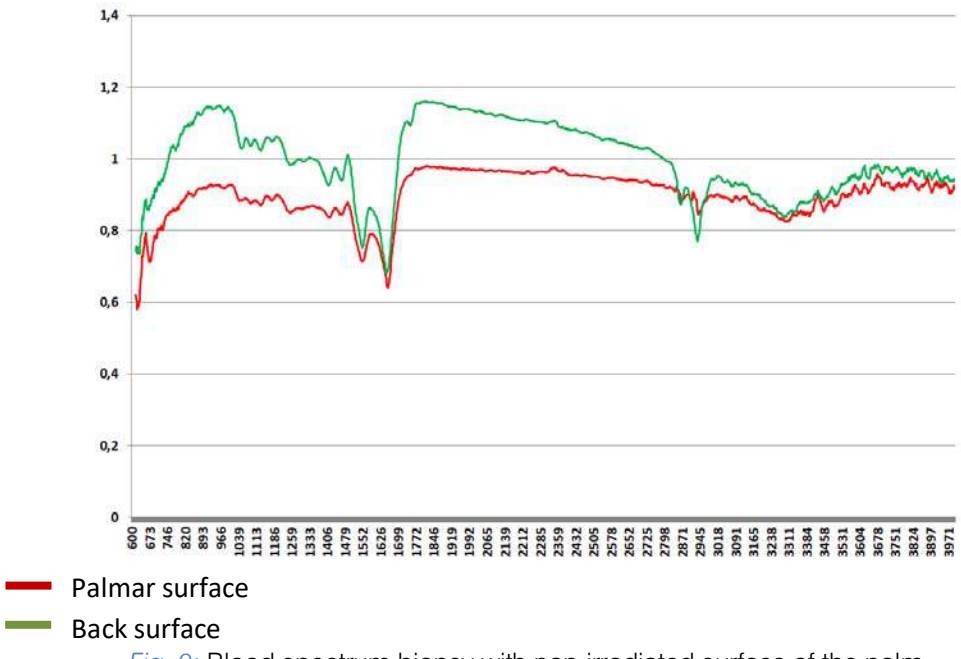


Fig. 9: Blood spectrum biopsy with non-irradiated surface of the palm

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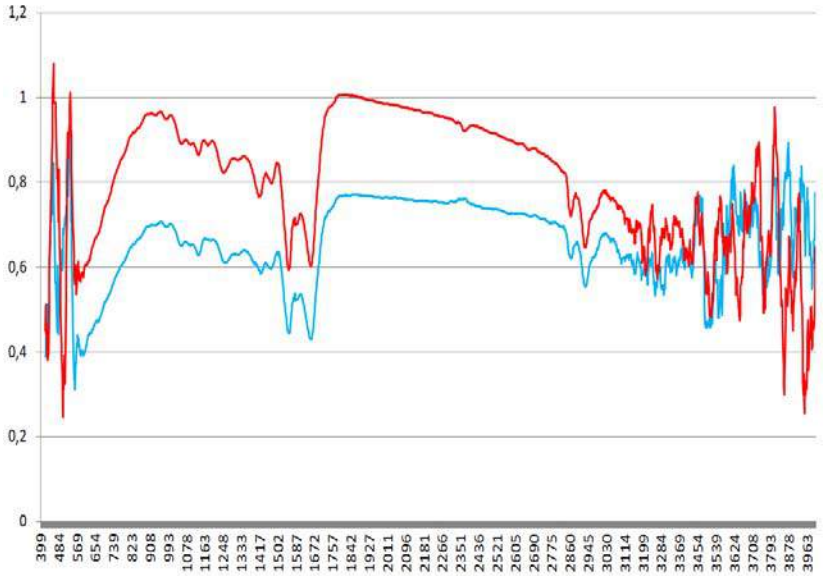


Fig. 10: Blood spectrum biopsy from the palm surface irradiated by yellow light during 10 minutes.



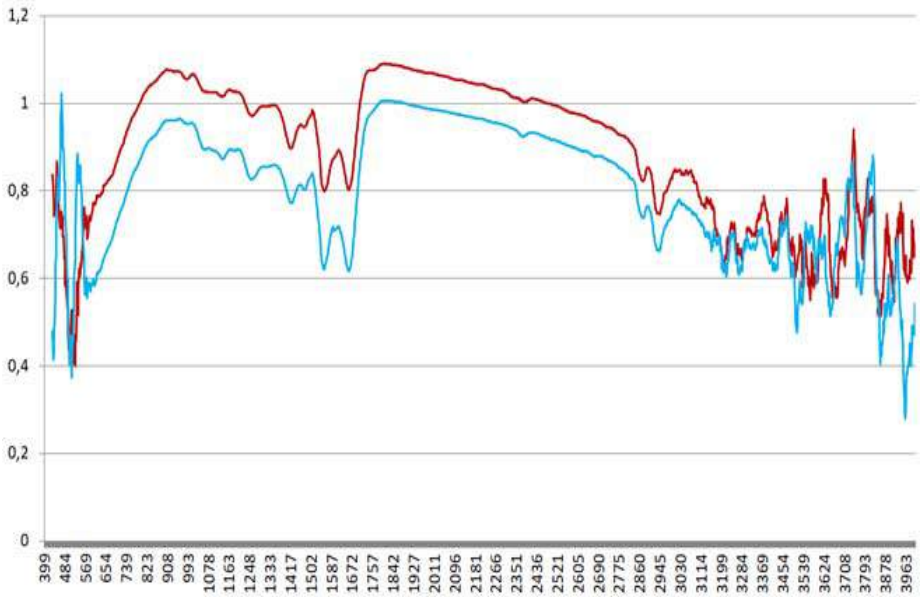
Fig. 11: Blood spectrum biopsy from the hand surface.

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Back surface after removal of two layers of skin with the adhesive tape
Back surface of the hand irradiated during 10 minutes.

Fig. 12: Blood spectrum biopsy from the hand surface.



Palm surface after removing two layers of skin by adhesive tape, irradiated by yellow light during 10 minutes.
Back surface after removing two layers of skin by adhesive tape, irradiated by yellow light during 10 minutes.

Fig. 13: Blood spectrum biopsy from the hand surface

Based on the results of experiments, we can assert that the experiments of G. A. Askarian of "increase in the passage of laser and other radiation through turbid physical and biological mediums" support our concept that an integral organism reacts to any external influence on the principle of "biological scanning tunneling microscope", i.e. the light passage through the entire thickness of palm is not due to the lateral displacement of blood and tissue, as stated by the author of the experiment, but to a layer-by-layer formation of evanescent waves deep in the palm with their subsequent increase at the exit of the opposite side of the palm. Also in favor of our concept, the conclusion of the author of the experiment is that the effect of illumination when pressing the palm is much stronger than when using polyurethane foam, and even the thicker parts of the palm – the flesh with blood, the area at the phalanges of the fingers is more permeable to light and more susceptible to illumination by compression than its central part.

Our concept of the tunnel effect of the integral organism emerging at exposure to low-energy

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electromagnetic waves is supported by the works of Russian and foreign scientists. They discovered the causes of emergence of the evanescent waves: Doctor of Physics and Mathematics, Professor German Nikolaevich Zhizhin, Doctor of Physics and Mathematics, Professor Vinogradov , V. N. Galynsky, A. I. Furs, L. M. Barkovsky, and some others. They believe that the interaction between photons and elementary excitations of the medium produces polaritons. The interaction between electromagnetic waves and excitations of the medium (phonons) leading them to bond becomes especially strong when their frequencies and wave-number vectors coincide (resonance). The bound waves are formed in this region, i.e. polaritons at the border of two media, and attenuate exponentially with the distance from the interface (near field). Phonon is a quasi particle introduced by the Russian scientist Igor Tamm representing a quantum of vibrational motion of crystal atoms.

Scientists discovered pseudo-particles traveling on the surface of light-sensitive materials.

Researchers from the Karlsruhe Institute of Technology, working together with scientists from the Fritz Haber Institute, Berlin, Germany, and Aalto University, Helsinki, Finland made a significant step towards implementing technologies for converting light into energy that can be used for the benefit of people [2,7].

Processes that convert light energy into energy of other types can and are gradually becoming the basis of technologies that will supply humanity with energy in the near future.

"The conversion of the energy of photons, particles of light, into electrical energy takes place in several stages," explains Professor Christoph Well, Head of the IFG Institute. First, light is absorbed on the surface of the light-sensitive material. The electrons leave their places as influenced by the energy of photons of light, leaving electron holes in their place, with which they immediately form quasi particles called polaritons. These polaritons exist only for a very short time, moving to the boundaries of the material, where they disintegrate into electrons and holes, which continue to move independently further on. The afterlife of these charge carriers already depends on the nature of the light-sensitive material used" [18]

It is known that the English physicist B. Josephson predicted in 1962 the DC and AC effects in the superconductor-dielectric contact on the basis of the Bardeen-Cooper-Schrieffer superconductivity theory.

Two superconducting layers separated by a negligibly thin insulator layer with thickness of a few atoms only will behave as a single system.

When a current is passed through the contact that does not exceed the critical value, there is no voltage drop on the contact (despite the presence of a dielectric layer).

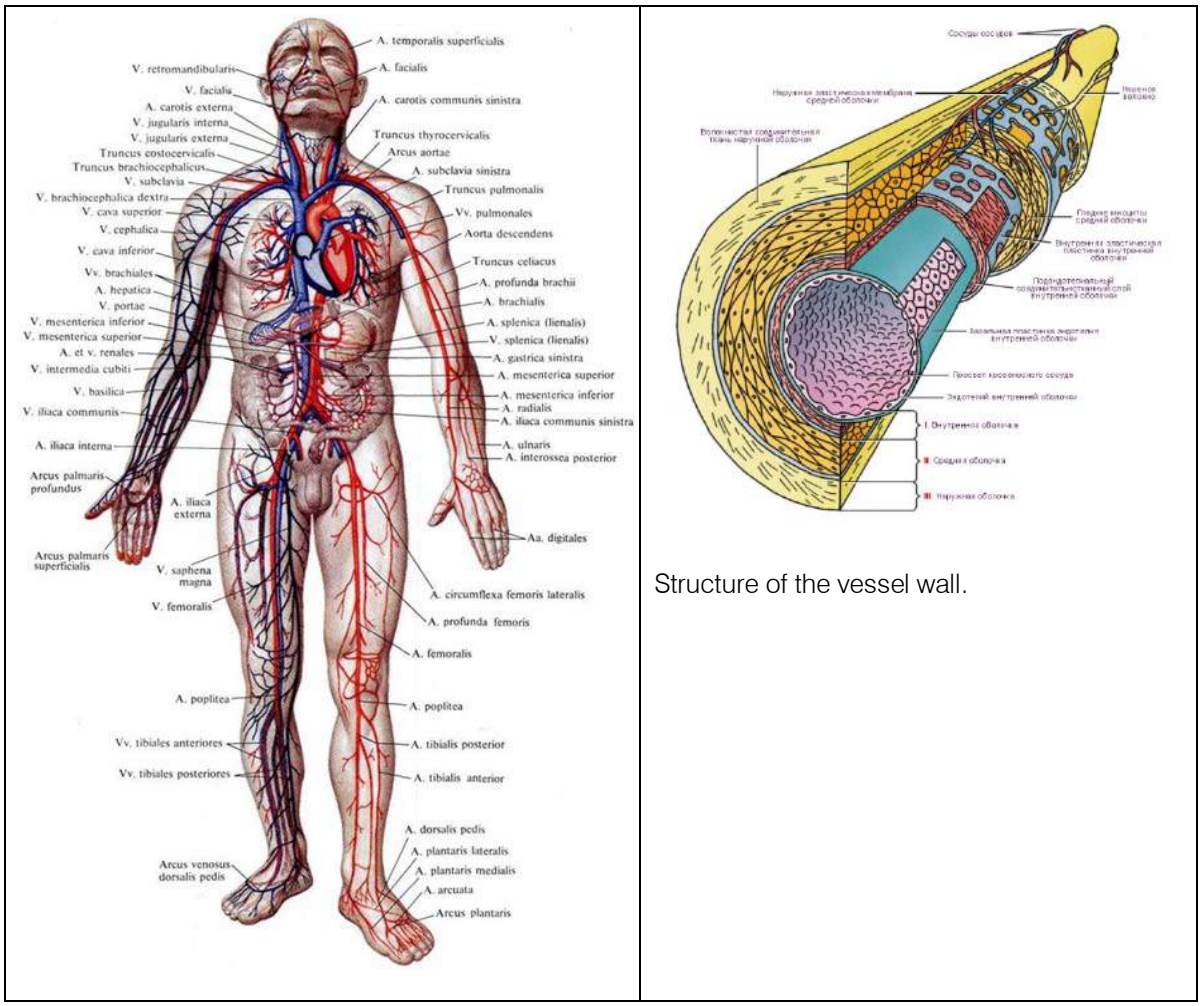
This effect is caused by the fact that the conduction electrons pass through the dielectric without resistance due to the tunnel effect. Electrons can pass the barrier even if there is no voltage applied to them (Cooper pair tunneling). The effect is called the DC Josephson effect [19].

If a constant voltage is applied on both sides of the passage, quantum mechanics predicts that Cooper pairs of electrons will move through the barrier first in one direction and then in the opposite direction, resulting in an alternating current, which frequency increases as the voltage grows. This effect is called the AC Josephson effect" [18,19].

According to the laws of physics, when an integral organism is exposed to electromagnetic waves, evanescent waves are formed from the outside of all capillaries, vessels, nerve trunks and roots, this is a set of "scanning tunneling biomicroscopes", and the effect of PVIP light on the organism is recorded using a "scanning tunneling photon microscope". Therefore, it should be considered that the animal organism is a single superconducting system working on the principle of the Josephson effect in superconductors.

In this regard, there is reason to assert that we have identified new, previously unknown mechanisms of action of weak electromagnetic waves on the integral organism and ways to record the organism's responses. In other words, the integral organism functions on the principle of a "scanning tunneling near-field biomicroscope", as it corresponds to the description of the device by Stephen Mendek from Germany.

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Structure of the vessel wall.

Fig. 15: Venous and arterial systems

The cardiovascular, nervous and lymphatic systems can be light guides and evanescent (attenuated) waves are also formed around them perpendicular to the outer surface of vessels, capillaries, and nerve roots when they are exposed to electromagnetic waves on any part of the skin surface, i.e. the integral organism enters the operation mode of the "scanning tunneling microscope", so evanescent IR spectroscopy of disturbed full reflection when touching the IR fiber is unique, not-damaging, not requiring special skin preparation -"blood spectrum biopsy", which reflects the entire information picture of the body at the atomic level. (A new advanced trend in Medicine). [12,13,14]

An international team of biologists discovered a natural compound that slowed ageing in healthy mice. The study was published in the Cell Metabolism Journal and EurekAlert issue (28.10.2016). Scientists believe that the deficiency of NAD (nicotinamide adenine dinucleotide) in the body is manifested with age. Thanks to NMN (nicotinamide mononucleotide), researchers were able to significantly slow down the physiological decline in ageing mice, as the level of metabolism in these animals was almost equal to that peculiar for young population [20,21].

Scientists believe that such impressive results are relevant for human beings as well.

Testing NMN containing drugs in humans has already begun in Japan. Scientists were able to use the NMN nucleotide, which is involved in the energy exchange of cells for the synthesis of the coenzyme NAD in animals' organisms. It is not possible to directly inject NAD into animals. NAD synthesis in the body slows down with age due to DNA damage. Experiments on mice showed that water-soluble NMN is absorbed into the blood within three minutes and later converted into NAD in tissues. Experts note that taking NMN by young mice has no effect. This compound (NMN), as scientists note, is found in a number of foods, in particular, broccoli, cabbage, cucumbers and avocado. The coenzymes NAD and NADP regulate the metabolism [20,21,22].

NADP is the reduced form of NAD and takes on the hydrogen and electrons of the oxidized compound and transfers them to other substances.

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Research conducted by scientists from the University of Washington showed that the substance NMN activates genes responsible for the production of certain proteins and sirtuins. The presence of these proteins in an increased concentration in the bodies of experimental rodents caused a significant slowdown in the age-related degradation of vision and metabolic processes in their bodies [21,22,23].

It is also worth noting that modern ideas about the regulation of cellular processes allow us to highlight a nitrogen oxide, which has a multifunctional physiological effect. This free radical can have both activating and inhibiting effects on various metabolic processes occurring in organisms of mammals and humans [20,21].

Intensive study of the biological effect of NO began in the 80's, When R. Furshgott and J. Zawadzki showed that the expansion of blood vessels under the influence of acetylcholine occurs only in the presence of endothelium – epithelial cells lining the inner surface of all vessels.

The substance released by endothelial cells in response not only to acetylcholine, but also to many other external influences resulting in vasodilation (as in the research of Professor K. A. Samoylova) was called "vasodilating endothelial factor". [20,21,24]

Soon later, it was proved that this substance is a NO gas and there are special enzyme systems in cells that are able to synthesize it.

In humans and mammals, nitrogen oxide is mainly formed as a result of the oxidation of the guanidine group of L-arginine amino acid with the simultaneous synthesis of another amino acid - citruline - under the influence of NO-synthase enzyme. The enzyme was called a synthase, not a synthetase, because it does not require ATP energy to work. [1,20,21,23]

Currently, there are three cell populations that are most studied with respect to synthesis and formation of NO: endothelium of blood vessels, nerve tissue cells (neurons) and macrophages - connective tissue cells with high phagocytic activity. In this regard, there are traditionally three main isoforms of NO-synthases (NOS): neuronal, macrophage, and endothelial (designated respectively as NO-synthase I, II, and III). Neuronal and endothelial isoforms of the enzyme are constantly present in cells and called constitutive, and the second isoform (macrophage) is inducible - the enzyme is synthesized in response to a certain external influence on the cell. [20,22,23]

Based on above, it should be emphasized that the second macrophage isoform (NOS) is synthesized under the influence on the integral organism of PVIP light at a wavelength of 480-3400 nm, according to the research of Professor K. A. Samoilova, there is also a basis to conduct fundamental research on discovering the increase in isoforms I and III under the action of PVIP light, due to the fact that according to our research, there is an instant impact of PVIP light on cardiovascular system and full coverage by the light exposure of the integral organism. [12,13,14,16]

Professor K. A. Samoilova claims in her research that the most important role in the stimulating effect of optical radiation on cells and tissues is assigned to two light – absorbing enzyme complexes that have the properties of oxidants-nicotine-adenine-dinucletide-phosphate oxidase (NADP-oxidase) and nucleotide-containing bioptero flavoprotei -NO-synthase. Exposed to action of visible and IR light, these enzymes localized in the cell membrane are activated and, using the ambient oxygen, produce its active forms (ROI) – superoxidanion, hydrogen peroxide, hydroxyl radical and nitrogen oxide (NO). These highly reactive molecules conduct a light signal from the surface of the irradiated cell to its nucleus, affecting specialized intracellular mechanisms for conducting the activation signal.

It has already been established that the formation of nitrogen oxide – NO-in the systemic circulation is the most important mechanism for such effects of visible and IR light as dilation of blood vessels and platelet disaggregation, failing which phototherapy could hardly be highly effective. [1]

Before proceeding to considering specific examples of the biological activity of NO in humans and animals, we should once again point out the multifunctional nature of its action, which can not be reduced only to "positive" or only to "negative" effects. [20,21,22]

The biological response to NO is largely determined by the conditions of its generation – where, when, and in what quantity this compound is produced. [19,23]

It is worth noting that to date, the localization, distribution of NO-synthase, non-enzymatic formation of nitrogen oxide, participation of NO in the regulation of the nervous system, in protective immunological reactions, participation of NO in the Central Nervous System (CNS), the role of nitrogen oxide as a regulator of cellular processes in the formation of multiple organ failure are underexplored.

Based on the above, it should be argued that there is a need to expand basic research on the basis of an academic research Institute with the involvement of specialists in physics, chemistry, cytology, physiology, biology and optical physics to create a methodology with the subsequent development of the subject and program on slowing down the natural ageing of a living organism.

In this regard, it should be considered that the results of the research of Professor K. A. Samoilova, published in the Materials of the scientific and practical

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conference "New trends in use of light therapy "Bioptron", Moscow, Yekaterinburg, April 2003, are the first data in the World on this problem.

The above concepts were confirmed with a high statistical accuracy by example of a new rehabilitation technology: "Underwater horizontal traction of the spine with underwater phototherapy" to solve an essential medical and social problem: treatment of patients with degenerative and dystrophic lesions of the lumbosacral spine with herniated protrusions of intervertebral discs, being one of the most common neurological pathologies worldwide.



Fig. 16: Underwater horizontal spine traction with underwater phototherapy through a fiber optic cable.

At the present stage of development of rehabilitation medicine, a wide inventory of medicinal and non-medicinal methods (physiotherapy, traction and manual therapy, reflexology, therapeutic physical training), as well as surgical (operative) treatment is used for the treatment of this category of patients.

However, it is not possible to achieve the desired therapeutic effect from the applied methods, due to the ineffectiveness of their combined use [3,4,5,6].

The least effect was received by the patients treated with the first method (control group) of drug therapy: improvement (no pain syndrome with the onset of persistent remission) was observed at 45.7% of patients, no changes (no clinical dynamics) - at 34.3% and deterioration (negative clinical dynamics) at 20%.

The results of therapy of patients of the second control group treated with the second method: combination of drugs with physical therapy is slightly higher than in patients of the first control group, namely: improvement (no pain syndrome with the onset of persistent remission) was 54.1%, no changes (no clinical dynamics) - 30.6% and deterioration (negative clinical dynamics) - 15.3%

It should be noted that the efficacy of treatment methods 3, 4 and 5, where one of the components of treatment is underwater spinal traction or underwater phototherapy, is significantly higher than in the first and second control groups, by 25-34%, 33-41% and 43-51% respectively.

It should also be noted that in the fifth group (n=128), improvement (no pain syndrome with the onset of stable remission) was observed in the first age group of patients aged 17 to 30 yerars, the fourth age group of patients aged 51 to 60y years, with the protrusion of HNP Z4-S1 into the spinal canal in cases of up to 5 mm and from 5 mm to 13 mm, 100% improvement was observed in patients of the second age group aged 31 to 40 years with the protrusion of HNP Z4-S1 into the spinal canal from 5 mm to 13 mm - 92.3%.

In three groups (3, 4 and 5), the largest share of patients without changes (no clinical dynamics) was found in the third group - 20.3%, and among the age groups, the largest share was found in patients of the third age group 41 to 50 - 7.8%.

The smallest share of patients without changes (no clinical dynamics) was represented by the patients of the fifth group (n=128) - 2.4%, and among the age groups, the largest share was also found in patients of the third age group aged 41 to 50 years - 1.6%.

As a result of comparisons of two control groups (I – n=175 and II-t=157) by age groups, it was found that the deterioration (negative clinical dynamics) was detected in the fourth age group of patients aged 51 to 60 years of the first control group n=175 - 6.8%, and the smallest share was represented by patients of the first age group of patients aged 17 to 30 years - 2.3% of the second control group n=157.

The analysis of long-term results of treatment of patients with dorsopathy, osteochondrosis of the lumbosacral spine with protrusion into the spinal canal of HNP L4-S1 up to 5 mm and from 5 mm to 13 mm for three years is **presented in table 25.**

It follows that the lowest incidence of relapse of severe pain syndrome was observed in groups 3, 4 and 5 - 20% in comparison with control groups 1 and 2 - 80%.

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It is worth noting that the inclusion of underwater traction of the lumbosacral spine and underwater phototherapy into the treatment regimen results in a lower incidence of pain relapse compared to the control groups treated with drugs only (first control group n=175) and a combination of drugs and physiotherapy (second control group n=157).

In other words, "the joint use of underwater horizontal spine traction with underwater phototherapy via fiber optic cable" contributes to restoration of impaired functions in 96-98% of patients with degenerative-dystrophic lesions of the spine, due to the regression of herniated protrusion of intervertebral discs by 30-50% and anti-inflammatory antioxidant effect of underwater phototherapy, but to date, such a regimen has not been used anywhere in the world for this pathology.

At the same time, repeated treatment during 5-7 years was undergone only by 0.5% of patients, and the pain passed in all patients after the first procedure. This is due to the unique combination of underwater horizontal spine traction with underwater phototherapy (yellow light with infrared light at wavelength of 480-3400 nm) via a fiber optic cable [11].

A high percentage of positive treatment outcomes, both immediately after the course of therapy and in the long term, indicates the high efficacy of the developed complex of rehabilitation medicine of underwater lumbosacral spine traction with underwater phototherapy.

The reliability of treatment outcomes is supported by the use of modern highly sensitive informative methods for assessing the condition of intervertebral discs (MRI and CT) and pathological morphological processes using blood plasma spectroscopy, blood spectrum biopsy from the skin surface for the first time in world healthcare practice. [1,14]

It should be noted that the presented rehabilitative technology surpasses all existing pharmaceutical products, non-drug treatment methods and occupies a well-deserved leading place in the primary prevention of degenerative and dystrophic spinal lesions in adolescents, sportsmen, drivers of road, railway and other vehicles with a driving time of more than 60 minutes per day.

The high efficacy of anti-inflammatory immunomodulatory, antiviral and antitumor effects of polarized light at 480-3400nm was confirmed by fundamental research of Russian and foreign scientists: Doctor of Biology, Professor K. A. Samoilova. Institute of Cytology of the Russian Academy of Sciences, Saint Petersburg, 2003; Doctor of Medicine, Professor L. N. Gerasimova, Burn Center of the N. V. Sklifosovsky Research Institute of Emergency Medicine, Moscow; Professor M. Lentz, Oxford University, UK; Professor L. Medinica, Institute of Dermatovenerology of the Clinical Center, University of Belgrade, Yugoslavia. [11,16]

A peculiarity of phototherapy performed using PVIP light is a very rapid "disappearance" of pro–inflammatory cytokines - tumor necrosis factor (TNF–α), interleukins-IL-6, IL-2 and IL-12 from the circulating blood, which is recorded just within 30 minutes after the first irradiation. So, at the initial increased content of TNF-α, it drops by 30 times, IL-8 – by 4-6 times, IL-2 – by 4-10 times and IL-12 - by 12 times (by the end of the treatment course). At the same time, the levels in plasma of anti–inflammatory cytokines - IL–10 and transforming growth factor - TGF-β1 increase, as well as a rapid six-fold increase in the blood of the most important immunomodulator - interferon-γ (IFN-γ) even at its initial normal levels. The most important function of this cytokine is to activate cellular immunity (functional state of monocytes, macrophages, natural killers, and cytotoxic T-lymphocytes), which primarily increases the body's antiviral and antitumor resistance [24].

Experience with PVIP irradiation of blood in vitro gives reason to associate all the described effects with the direct action of light on the blood. In experiments of all designs, light not just stimulates, but regulates the cytokines levels.

Also, there is also direct contact in vivo with the cardiovascular system (blood) through perspiration.

This is an instantaneous effect on the cellular, supramolecular (atomic) level [13,14,16].

In this regard, there is reason to assert that the system of underwater horizontal spine traction with underwater phototherapy, for the primary disease prevention in adolescents, sportsmen and improving the quality of life of patients with degenerative and dystrophic lesions of the spine, deserves to be promptly introduced into the practice of rehabilitation centers, medical and sports dispensaries, health resorts, departments of therapeutic physical training of healthcare institutions and boarding houses.

A human being is a particle of Nature, and all biological processes proceed in him or her in accordance with a strict "program", in the strictest hierarchy from elementary particles to complex structures [12,13].

There are no two identical elementary particles in nature, hence the supramolecular formations consisting of them up to the Cosmos itself. As exemplified by a living organism in any system (muscular, circulatory, nervous, cardiovascular, etc.), there are no two identical cells either in content or in form, because there would be no muscle contraction, impulse transmission, intracellular and intercellular movement, i.e. the complete absence of visible life activity, i.e. movement with super-low speeds at the supramolecular level, but our cognition of the same is limited by the range of human knowledge [13,14].

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The intracellular structure of any system is unique, so the intracellular energy is. Therefore a difference of intercellular energy exists as a source of constant endless movement with the huge endless range of speeds, which creates a cyclical nature of processes of "matter-energy" transition from one state to the next ones. This should be considered by a specialist physician, when prescribing drug therapy to patients, otherwise it may result in various complications and addiction to drugs (disorders of organs and systems functions, development of drug addiction, allergies to drugs) [13,14,25].

It is known that "the concept of radiation hormesis was introduced to biology in the 80's and, as homeopathy postulated, while large doses of radiation have adverse effects on living organisms - inhibit cell division, growth and development, then small doses stimulate almost all physiological processes." The effects associated with the manifestation of the stimulating effect of low doses of radiation were called radiation hormesis. [26]

In this regard, there is a reason to believe that any physical factor affects the body through liquid perspiration from the skin surface. The cardiovascular system instantly connects the physical factor to all organs and systems at the supramolecular level. The same instantaneous connection is carried out by the "tunnel effect", but the current level of technological development does not allow to differentiate them.

According to Einstein's famous formula stating the "mass-energy equivalence" and thus justifying the process of mutual transformation of mass and energy ($E=m\ c^2$), the real primary quantum touch of pathological cells with the physical factor selected for treatment is completed.

Weak physical effects are more selective and require a very fine adjustment of parameters of the same, in order to implement an interaction contributing to restoration of the disturbed specific biological process [13,14].

A selective, correct method of a therapeutic physical factor application for a specific intermediate state of the integral organism in the course of its cyclic development at pathology provides for the rejection of use of high-energy parameters of the selected physical factor. This is necessary to prevent the simultaneous destruction of intermediate cyclic states of weakened morphological supramolecular formations of the body and strong pathological supramolecular formations, which is a gross interference with the biological cyclic processes of the body.

This can lead to complete or partial irreversible states of organs and systems of the integral organism. In this regard, it should be argued that the application of "established medicamentous standards for diseases" for all patients with the same diagnosis is anti-scientific and extremely dangerous.

Due to the fact that any disease is unique for each patient: etiology, pathogenesis, clinical findings, disease outcome, consequences for the integral organism in the future, because even two identical pathogens of any disease do not exist in Nature.

III. Conclusion

Development of a system of rehabilitation treatment of patients with degenerative and dystrophic lesions of the lumbosacral spine with herniated protrusions of intervertebral discs is an challenging medical and social problem (this pathology is one of the most common neurological diseases in the world and, especially, in Russia).

The combined use of underwater horizontal spine traction with underwater phototherapy can contribute to restoration of impaired functions in patients with degenerative and dystrophic lesions of the spine, but to date, such a complex has not been used for treatment of this pathology.

From the point of view of rehabilitation medicine, this work implements a comprehensive therapy of herniated protrusions of the intervertebral discs of the lumbosacral spine through a new system of rehabilitation treatment by underwater horizontal spine traction and underwater phototherapy.

The therapeutic effect on the body of polychromatic visible and infrared polarized light through the water environment, which may be determined by its activating effect on water, was proved for the first time under experimental conditions. The author a) showed a remarkable regression of herniated protrusion of the intervertebral disc of the lumbosacral spine, when using the developed system of rehabilitation treatment. b) substantiated the expediency of using and a) proved a high clinical efficacy of the combined use of underwater horizontal spine traction and underwater phototherapy for treatment of degenerative and dystrophic spine lesions.

In a comparative perspective, a high efficacy of rehabilitation technology applied according to the author's method was established in comparison both with drug therapy and combination with other known methods of physiotherapy and drug treatment.

The results of experimental and clinical data confirm the clear advantage of the physical factors use over drug therapy in case of pathology of the musculoskeletal system.

Therefore, "Physiotherapy science" should take its rightful place among the leading scientific disciplines of the world medical science.

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I dedicate my modest work to my dearest mother
Princess of the Great Alania, Averi Gabolaevna Kulova-Bitsoeva.
With undying love, son Vladimir.

Soul covenants of my dearest mother:



"Ask God in your prayer to heal the people that begraced you, always be warm-hearted and kind in praise of the Heavenly King"

"Look into the eyes and face of the servant of God, where you can see his distress, do not look onto his hands – you will drown in unholy temptations and will not be able to cure neither his soul, nor his body".

"Keep the secrets of the people who shared them with you and do not use them for your Glory".

"Do not chase the "Glory", it can be neither overtaken nor embraced, it finds the ones worthy of it".

"Be happy with the happiness of the others, feel the people's distress and provide them with diligent help without waiting for request".

"Your way must always be lit up and shown by your heart and mind".

I express deep gratitude to my family, especially to my dear granddaughter Dzerassa Margieva.
As well as to Professors:

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I remember my Great teachers with deep gratitude:

Professor E. P. Semenov, Professor V. S. Ulashchik and Academician Jaromir Hrbek. May the memory of them live forever.

Conclusions

1. It was established that the impact of energy of any physical factor is dosed and regulated (physiodynamics) with the help of nanotechnologies and its path to each molecule of the integral organism (physiokinetics) is easily traced without disturbing supramolecular structures and any negative consequences.
   Modern world pharmaceutical science does not have such a high level of pharmacodynamics and pharmacokinetics.
2. We discovered that the bioelectric potential for each human being is strictly individual both in norm and pathology. In this regard, any nosology causes in each individual a deviation of his or her bioelectric potential in accordance with the stage of disease development, i.e. development of intermediate states of the body with certain disorders of its supramolecular structures.
3. We believe that there is a need to expand basic research on the basis of an research institute with the involvement of specialists in physics, chemistry, cytology, physiology, biology and optical physics to create a methodology with the subsequent development of the subject and program on slowing down the natural ageing of a living organism.
4. It is established that the created new system of rehabilitation technology of underwater horizontal spine traction with underwater phototherapy through fiber optic cable exceeds all existing pharmacological means, other non-medicinal methods of treatment and occupies a well-deserved leading place in the primary and secondary prevention of degenerative and dystrophic spine lesions in adolescents, sportsmen, drivers of all types of vehicles. There are no analogues in the world healthcare practice.
5. It was established, that the system of underwater horizontal spine traction with underwater phototherapy, for the primary disease prevention in adolescents, sportsmen and improving the quality of life of patients with degenerative and dystrophic lesions of the spine, deserves to be promptly introduced into the practice of rehabilitation centers, medical and sports dispensaries, health resorts, departments of therapeutic physical training of healthcare institutions and boarding houses.

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6. It was established that any disease is unique for each person: aetiopathogenesis, clinical findings, state of intermediate cyclic morphological supramolecular formations of organs and systems of the body.
   Therefore, application of "established medicamentous standards for diseases" for all patients with the same diagnosis is anti-scientific and extremely dangerous.

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6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

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It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

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Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

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- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
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2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

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Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

INDEX

A

Abscisic • 6
Alleviate • 17
Alveolar • 35
Apical • 7
Apoptosis • 46, 487

C

Coagulation • 33, 34
Colitis • 2, 5, 6, 7, 8, 9, 10, 46
Colonoscopic • 7
Combat • 12, 45
Corticosteroids • 36, 37, 40
Counteraction • 49, 50

D

Devoid • 3

E

Elicit • 5, 34
Endogenously • 45
Eradicating • 50
Erythema • 40, 42, 43
Evanescent • 1, 3, 1, 2, 1, 2, 1
Exudation • 35

G

Geriatrics • 14, 16

H

Hypoxia • 10, 46, 47, 50

I

Innate • 1, 2, 10, 34, 38, 45, 46, 48, 50
Intermittent • 15

M

Milieu • 1
Monoclonal • 5, 36, 37, 38, 39
Morass • 17

N

Necrosis • 2, 10, 34, 48, 50, 4

O

Opacity • 37
Ounce • 15

P

Palliating • 18
Phalanges • 2, 1
Polaritons • 2
Predilection • 40, 41
Predominantly • 3
Proliferation • 34, 37, 45, 46, 47, 50
Propia • 2
Protrusions • 1, 2, 3, 5

R

Recombinant • 7, 37
Regimens • 14
Relapsing • 1
Restorative • 15
Rodents • 5, 2

S

Sepsis • 47
Spleens • 47
Splenic • 47
Sputum • 48
Squandering • 17
Suppressants • 2
Synergistic • 39, 48, 49

T

Tunneling • 1, 2, 1, 2, 1

U

Unequivocally • 16



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