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Licensing and Access to Drugs

Phenolic Compounds from Plants

Highlights

Enhance the Community Pharmacy

Pharmacological Study of Chitraka

Discovering Thoughts, Inventing Future

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By R. A. Khusainova, K. A. Ubaydullaev, N. M. Rizaev & M. O. Akromov

Abstract- The study of antibiotics as a potential drug, in addition in order to develop effective methods for assessing quality in preclinical stage includes the establishment of stability and expiry date. This study regulatory requirement is necessary to establish the time during which the substance remains unchanged physical, chemical, biological properties, i.e. suitable to all requirements of regulatory documentation. Justification of the established expiry date of the substance is included in the section of the registration dossier on the methods of quality assessment. The purpose of this study is to establish the expectancy duration and stability of the antibiotics of the cephalosparin group of a number produced by “Jurabek Laboratories” JV LLC.

Keywords: stability, intralin, accelerated aging, IR spectrum, UV spectrum, HPLC.

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STUDYOFSTABILITYANDEXPIRATIONDATEOFINTRALINPOWDERINBOTTLES0.5AND1.0G

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Study of Stability and Expiration Date of Intralin Powder in Bottles 0.5 and 1.0 G

R. A. Khusainova [α], K. A. Ubaydullaev [σ], N. M. Rizaev [ρ] & M. O. Akromov [ω]

Abstract- **The study of antibiotics as a potential drug, in addition in order to develop effective methods for assessing quality in preclinical stage includes the establishment of stability and expiry date. This study regulatory requirement is necessary to establish the time during which the substance remains unchanged physical, chemical, biological properties, i.e. suitable to all requirements of regulatory documentation. Justification of the established expiry date of the substance is included in the section of the registration dossier on the methods of quality assessment. The purpose of this study is to establish the expectancy duration and stability of the antibiotics of the cephalosparin group of a number produced by "Jurabek Laboratories" JV LLC.**

Keywords: stability, intralin, accelerated aging, IR spectrum, UV spectrum, HPLC.

I. Introduction

Stability (sustainability) is a factor in the quality of medicines. The criterion for the stability of a medicinal substance is the preservation of its quality, i.e. appearance, solubility, authenticity, good quality and quantitative content. The decrease in the quantitative content of the pharmacologically active substance in the drug confirms its instability. The decrease in the quantitative content of the drug by 10% should not occur within 3-4 years in the finished dosage forms.

To increase stability, chemical processes occurring during storage of drugs are investigated and methods are created to inhibit these processes. The solution of these problems is possible only on the basis of the development of methods for analyzing medicinal substances in the presence of their decomposition products. The results of these studies are taken into account when developing the technology of obtaining drugs and ND.

Products of organic synthesis make up a significant part of the arsenal of medicines of modern medicine. Despite the significant number of drugs used in medical practice, the search for more effective and safe ones is constantly underway. Largely, this refers to groups of drugs used to treat inflammatory processes caused by bacterial microflora [1, 2].

II. Material and Methods

Material of the study is the substance "Intralin" - (cefazolin sodium salt/5-thia-1-azabicyclo [4.2.0] octa-2-en-2-carboxy, 3-[[(5-methyl-1,3,4-thiadiazole-2-yl) thio] methyl]-8-oxo-7-[[(1H-tetrazole-1-yl) acetyl] amino]-, sodium salt (βY-trans)-) 0.5 or 1,0 g, powder for the preparation of injection solutions released by JV "Jurabek Laboratories" LLC.

The experiments were carried out on 3 series of antibiotics obtained in the laboratory by the methods. All samples of antibiotics were pre-analyzed in accordance with the requirements of the FS project developed by the author.

- IR spectra were obtained by Protégé 460 "Nicolet Instruments Corporation" (USA);
- UV spectra were obtained by UV-spectrophotometer 8453 by Agilent Technologies (Germany);
- HPLC chromatograms were obtained by UV-spectrophotometer HPLS 1260 by Agilent Technologies (Germany);
- Used thermostat TOVL-80.
- Auxiliary equipment and reagents were also used in the work.
- Used reagents, solvents, indicators that meet the requirements of the Global Fund XI ed. Test methods for authenticity and quantification, developed earlier by the authors.

In determining the expiration dates, they were guided by the requirements of the Global Fund XI and the Interim Instruction I-42-2-82. According to these documents, the establishment of stability is possible using the following methods:

– Test under long-term storage conditions;
– Testing under conditions of "accelerated aging" according to the Interim Instruction I 42-2-82.

The method of "accelerated aging", based on the law of van't Hoff, establishes the relationship between the shelf life of the substance and storage temperature

$$C = A^{\frac{tэ-txp}{10}} \frac{tэ - txp}{10}$$

Where, experimental substance series:

tэ is the temperature of experimental storage.

t_{xp} - storage temperature.

A is the temperature coefficient of the chemical reaction rate when the temperature increases by 10 °C (assumed 2) [3].

Investigations were carried out on 3 series of cefazolin substance (040113, 070113, 100113) at an

Author α σ ρ ω: Tashkent Pharmaceutical Institute, Tashkent, Uzbekistan. e-mail: author.uzb@mail.ru

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experimental storage temperature of 60 °C. Samples were placed in vials of 0.5 or 1.0 g of the drug from a glass tube of the type FO-1-15 or 00-1-20 according to TU 64-2-10-87 or imported in accordance with ISO 8362-1 and ISO 8362-4, hermetically sealed with stoppers of rubber stamps I-51ili 52-599 / 1, or IR-119po TU 38.006108-90 or imported according to ISO 8362-2, compressed with aluminum caps of type K-2, as per ISO 6462-686 or imported according to ISO 8362-6. Quality control was carried out at time intervals (11.5 days), equivalent to 6 months of storage in natural conditions according to the indicators given in table 1 [4,5].

Table 1: Specification: "Intralin 0.5 or 1.0 g" powder for the preparation of injection solution produced by J V Jurabek Laboratories LLC Uzbekistan

Indicators	Methods	Standard
Description	Visual	Powder white or almost white, very hygroscopic
Solubility	Visual	Easily soluble in water, very little soluble in 96% alcohol
Authenticity	Infrared spectrometry	1. IR absorption spectrum of drug sample obtained in disks with potassium bromide (about 2 mg of the drug in 200 mg of potassium bromide) from 4000 to 450 cm "should correspond to the spectrum of the RSO cefazolin sodium salt (about 2 mg of the RSO cefazolin sodium salt in 200 mg of potassium bromide).
	UV Spectrophotometer	2. The ultraviolet absorption spectrum of the solution in the region from 220 to 350 nm should have an absorption maximum at a wavelength of 272+2 nm.
	Chemical reactions	3. The drug gives a characteristic reaction to sodium.
Quantitative content	HPCL	From 850 to 1050 mcg, calculated on the dry matter

The results of the experiment (Table 2) showed that the cefazolin substance remains stable for 69 days of experimental storage, which corresponds to 1104 days of storage under natural conditions, calculated according to the van't-Hoff rule:

$$C = A^{\frac{t_э - t_{хр}}{10}} = 2^{\frac{60-20}{10}} = 16 - 16 \cdot 69 = 1104 \text{ сут.}$$

compliance rate.
Hence, the shelf life, which is 3 years.
Storage temperature, which allows to ensure the established shelf life is:

$$t_{хр} = t_э + \frac{10}{lgA} \cdot lg\frac{C_э}{C} = 60 + \frac{10}{lg2} \cdot lg\frac{69}{1104} = 20\,°C$$

The maximum allowable storage temperature is:

$$t_{макс.доп.} = 20\,° + \frac{10}{lgA} \cdot lg\frac{C_э}{2 \cdot 365} = 20 + \frac{10}{lg2} \cdot lg\frac{1104}{730} = 26\,°C$$

Thus, as a result of the studies conducted by the method of "accelerated aging", the shelf life and temperature storage of the cefazolin substance has been established.

Thus, a preliminary shelf life of 3 years can be established.

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Table 2: The results of studies on the stability of drug cefazolin by the method of "accelerated aging"

Series	Life expectancy, in days	Description	Authenticity			Quantitative content, %
			IR-spectrum	UV spectrum	Characteristic reaction to sodium	
1	2	3	4	5	6	7
040113	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of RSO cefazolin	Maximum at 272+2 nm.	Yellow precipitate	99,9
	11,5	- // -	- // -	- // -	- // -	99,85
	23	- // -	- // -	- // -	- // -	99,86
	34,5	- // -	- // -	- // -	- // -	99,84
	46	- // -	- // -	- // -	- // -	99,96
	57,5	- // -	- // -	- // -	- // -	99,75
	69	- // -	- // -	- // -	- // -	99,71
070113	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272 + 2 nm.	Yellow precipitate	99,95
	11,5	- // -	- // -	- // -	- // -	99,97
	23	- // -	- // -	- // -	- // -	99,85
	34,5	- // -	- // -	- // -	- // -	99,84
	46	- // -	- // -	- // -	- // -	99,85
	57,5	- // -	- // -	- // -	- // -	99,72
	69	- // -	- // -	- // -	- // -	99,70
100113	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,90
	11,5	- // -	- // -	- // -	- // -	99,85
	23	- // -	- // -	- // -	- // -	99,82
	34,5	- // -	- // -	- // -	- // -	99,91
	46	- // -	- // -	- // -	- // -	99,93
	57,5	- // -	- // -	- // -	- // -	99,75
	69	- // -	- // -	- // -	- // -	99,72

The study of the stability of cefazolin was also carried out by the method of long-term storage. For this, cefazolin series 151210, 171210, and 201210 were stored in dry and dark place that ground-glass jars with ground glass stoppers at room temperature. Quality control was carried out on the main indicators, at intervals equal to 1 year of storage. Studies (tab. 3) showed that the stability of the substance cefazolin in long-term storage conditions is maintained for at least 3 years.

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Table 3: The results of studies on the stability of drug cefazolin in vivo

Series	Expiry date, in years	Description	Authenticity			Quantitative content, %
			IR spectrum	UF spectrum	characteristicre actiontosodium	
1	2	3	4	5	6	7
151210		White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,40
	1	- // -	- // -	- // -	- // -	99,81
	2	- // -	- // -	- // -	- // -	99,79
	3	- // -	- // -	- // -	- // -	99,72
171210	0	White or almost white crystalline powder; odorless	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,81
	1	- // -	- // -	- // -	- // -	99,78
	2	- // -	- // -	- // -	- // -	99,73
	3	- // -	- // -	- // -	- // -	99,69
201210	0	White or almost white crystalline powder; without smell	The spectrum corresponds to the spectrum of cefazolin RSO	Maximum at 272+2 nm.	Yellow precipitate	99,87
	1	- // -	- // -	- // -	- // -	99,81
	2	- // -	- // -	- // -	- // -	99,78
	3	- // -	- // -	- // -	- // -	99,75

III. Conclusion

1. It was found that the stability and shelf life of the investigated drug, established by the method of "accelerated aging" at a temperature of 60 °C, is not less than 3 years, and the storage temperature is from 20 to 26 °C.
2. It is established that the substance of cefazolin in the conditions of long-term storage at room temperature in a dark place is not less than 3 years.

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5. In accordance with modern requirements, in accordance with the General technical regulation on the safety of medicinal products (Appendix to the Decree of the KMRUz dated October 27, 2016 No. 365).

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Pharmacological Study of Chitraka Haritaki Avaleha & Shikhari Taila

By Atara Achyuta, Manjusha R. & Nariya Mukesh

Abstract- *Chitraka Haritaki Avaleha* is a *Leha Kalpana* (semisolid preparation of drugs, prepared with addition of jaggery & boiled with prescribed decoction) specifically indicated for oral use in treatment of nasal disorders in Ayurveda. *Shikhari Taila* is a formulated oil with the herbs having medicinal values. Use of *Shikhari Taila* for *Nasya* (one of the Panchakarma procedure mentioned in Ayurveda) in *Nasa Arsha* (Nasal polyposis) has been mentioned in Ayurvedic texts, but no work has been done at any of the PG centers of Ayurvedic Institutes. Both the drugs are having anti histaminic & anti inflammatory properties. Hence the present study was designed to ascertain whether it is possible to obtain experimental data to support the clinical study; and helps to prove the above theory, according to criteria of modern pharmacology too.

Keywords: *chitraka haritaki avaleha, shikhari taila, anti histaminic, anti inflammatory.*

GJMR-B Classification: *NLMC Code: QV 37*



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Keywords: *chitraka haritaki avaleha, shikhari taila, anti histaminic, anti inflammatory.*

I. Introduction

Pharmacology is an applied science. It forms the backbone of rational therapeutics, correct and skillful application of the drugs is impossible without a proper understanding of their basic Pharmacology. It is the science of drug action, has helped to elucidate many basic physiological and pathological mechanisms in health and disease. Various animal experimental models have been designed to study the effect of drugs on living organisms and isolated tissues. These give an insight about where and how a drug act, the mode of action of a drug, its effect on various body systems and probable adverse effects before administration of a drug. Therefore, the object of pharmacology is to provide such scientific data in animals as well as humans, which forms the basis of rational therapeutics.[i] Man occupies a supreme position among all the living creatures. Hence before administering drug to him it is desirable to experiment on other animals.

In the ancient Ayurvedic literature, lots of references are available regarding the testing of the drug and food on the animal for the safety of the mankind. The role of research in Ayurveda is not only to elucidate the principles of Ayurveda but also, to explain them in terms of modern parameters. A drug is accepted by modern science only if it has been proved safe by experimental studies. Drugs selected in the present study, i.e. *Chitraka Haritaki Avaleha* and *Shikhari Taila* are having anti histaminic & anti inflammatory properties.

Author: *e-mail: achyutaa250@gmail.com*

Hence the present study was designed to ascertain whether it is possible to obtain experimental data to support the clinical study; and helps to prove the above theory, according to criteria of modern pharmacology too. It was carried out with following aims & objects.

II. Plan of Study

Aims & Objectives

(1) To evaluate the Anti–inflammatory activity of *Chitraka Haritaki Avaleha* & *Shikhari Taila.*

(2) To evaluate the anti-histaminic activity of *Chitraka Haritaki Avaleha* & *Shikhari Taila.*

III. Materials and Methods

The animals for experimental study were obtained from animal house attached to pharmacology laboratory, IPGT and RA, Jamnagar, Gujarat, India. The experiment was carried out after obtaining permission from institutional animal ethics committee vide permission (IAEC/15/2013/38) as per CPCSEA guidelines. The dose for the experimental study was converted based on the body surface area ratio by referring table of Paget and Barnes (1969).

a) Test Drugs

i. *Source of Drug*

Both the formulations *Chitraka Haritaki Avaleha* and *Shikhari Taila* were prepared by the Gujarat Ayurved University Pharmacy for administration to the experimental animals. The *Avaleha* was taken and a stock solution was prepared freshly just prior to administration to animals by adding adequate quantity of water and used for the experimental purposes.

ii. *Test Drugs*

- *Chitraka Haritaki Avaleha.*
- *Shikhari Taila.*

b) Posology

i. *Dose Derivation*

Use of *Shikhari Taila* for *Nasya* in *Nasa Arsha* (Nasal polyposis) has been mentioned in *Chakradatta Nasarogaadhikara*.[ii] Dose for *Nasya* kept was 10 *Bindu*[iii] (drops) in each nostril for 6 sittings. *Chitraka Haritaki Avaleha* has been mentioned in *Chakradatta* [iv] & *Yogaratnakara* [v] in treatment of chronic rhinitis/sinusitis. Dose of *Chitraka Haritaki Avaleha* was 10 gms.[vi] twice a day for 3 months. Considering adult human dose of

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both samples, the dose for experimental study was calculated by extrapolating the human dose to animal dose based on the body Surface Area Ratio.

ii. *Dose calculation for Rat (in anti-inflammatory activity)*

The suitable rat dose was calculated by referring the table of Paget and Barnes (1969).

(1) *Test drug:* Chitraka Haritaki Avaleha

Rat dose = Adult human dose × 0.018 (conversion factor for rat weighing 200g)

= 20 g × 0.018

= 0.360 gm/ 200gm rat (360 mg/200gm rat)

= 1.8 gm/kg body weight

(2) *Test drug:* Shikhari Taila

Rat dose = 48 ml × 0.018 (conversion factor for rat weighing 200g)

= 0.864ml/ 200gm rat

= 4.3 ml/kg body weight

c) The Animals

i. *Animal Selection*

An overnight fasted Guinea pig was sacrificed to obtain fresh ileum for anti histaminic study & Charle's Foster albino rats of either sex weighing between 200 ± 35g were selected for anti inflammatory activity with the following conditions:

- *Husbandry conditions:* Standard husbandry conditions with ambient condition of temperature and relative humidity was maintained.
- *Diet:* Amrut brand rat pellet feed. Drinking water was given *ad libitum.*
- *Acclimatization period:* All the selected animals were kept under acclimatization for one week before experimentation.
- *Identification:* Animals were marked with saturated picric acid solution for proper identification.

ii. *Groups*

The rats were divided into three groups of six rats in each group;

- Group I (Water Control): Distilled water (10 ml/kg, po)
- Group II (Avaleha Group) 1.8 gm/kg, p.o.
- Group III (Taila Group) 4.3 ml/kg; p.o.

iii. *Route of drug administration*

The test drugs were administered through oral route for five days with the help of gastric catheter sleeved onto a syringe.

iv. *Statistical Analysis*

The data generated during the study was subjected to student 't' test Unpaired and Paired't' test used for assessing the significance of the results. Results within different groups at value of $P<0.05$ is considered as statistically significant.

d) Preparation

i. *Instruments Used*

Weighing balance, cotton, syringe, needle, catheters, centrifuge, refrigerator, plethysmograph, isolated organ bath, kymograph and other minor accessories.

ii. *Chemicals used*

- 1% carrageenan aqueous solution was used for anti-inflammatory study.
- Tyrode & Histamine solutions were used for anti histaminic study.

iii. *Experimental Model*

Experiment 1: Anti-inflammatory activity - Carrageenan induced paw oedema.

Experiment 2: Antihistaminic activity.

e) Anti-Inflammatory Activity

i. *Carrageenan induced paw oedema*

It is the basic test for screening anti-inflammatory effect. Carrageenan injection produces marked swelling of the paw and anti-inflammatory drugs are supposed to suppress this swelling. Method of Winter *et al.* (1962) was adopted to screen the anti-inflammatory activity of *Chitraka Haritaki Avaleha* and *Shikhari Taila* against carrageenan induced paw oedema in rats.

Rats were provided with food and tap water up to the start of the experiment. Initially left hind paw volumes up to the tibio-tarsal articulation were recorded by Using a Plethysmograph. The Plethysmograph employed, consists of 10 ml glass vessel (25 mm x 65 mm) fixed to 2 ml glass syringe through pressure tubing. About 5ml mercury was filled in the syringe and the mercury level was adjusted to zero mark on the micropipette. The space between the zero mark and the fixed mark of the glass vessel was filled with water and few drops of teepol. The initial level of fluid was adjusted and set at zero. The paw was immersed in water exactly up to the tibio-tarsal joint. The increased level of water in the glass vessel was adjusted to the prefixed mark by releasing the pressure of the connected syringe. The level where water and mercury interface in the micropipette was recorded as paw volume.

ii. *Procedure*

One hour after drug administration, oedema was produced by injecting 0.1 ml freshly prepared 1% carrageenan in sterile saline solution to the sub-plantar aponeurosis of the left hind limb. The rats were administered with the tap water in the dose of 2 ml/l00g body weight to ensure uniform hydration. This is supposed to minimize the variation in oedema formation. The paw volume is recorded at the interval of l hr, 2 hr, 3 hr and 6 hr.

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If the percentage of increase in paw volume is significantly less in test drugs administered groups in comparison to control group then the drugs were considered to possess anti- inflammatory activity.

f) Antihistaminic Activity

i. *Effect of test drug on the Guinea pig ileum (in vitro)*

There is increasing evidence that the airway epithelium may play an important role in airway inflammation, as disturbance of the epithelium, such as may occur on exposure to chemical, physical and immunological stimuli, can lead to the release of proinflammatory cytokines. There is an increased number of epithelial mast cells in nasal polyps. Total histamine levels in polyps are far higher than in other tissues (l00-1000 times that of plasma) .The release of histamine may be an important factor in causing plasma exudation. [vii] Because of this reason the test drugs were assessed for anti-histaminic property in isolated guinea pig ileum preparation.

ii. *Procedure*

This experiment was set-up following standard procedure. A Guinea Pig was sacrificed by cervical dislocation and a piece of ileum was excised out. It was set up in an isolated organ bath assembly following the standard procedure. The organ bath containing 40 ml of tyrode solution was maintained at 37 °C temperature and was aerated with oxygen. Tissue responses were recorded with an isotonic frontal writing lever system with 1:7 magnification and 500 mg initial tension on a smoked drum attached to a kymographic recording drum after 30 minutes of initial resting. Initially the dose responses were recorded with a standard spasmogenic drug i.e. histamine to select a dose producing sub-maximal response. Standard response was taken with histamine with a dose of 200 µg/ml of bath fluid. The effect of test drugs *per se* if any and the modulatory effect on the tissue response to histamine were recorded.

IV. Observation

a) Anti-Inflammatory Activity

Table 1: Anti-Inflamatory Effect of *Chitraka Haritaki Avaleha* & *Shikhari Taila* on Carrageenan Induced Paw Oedema in Albino Rats

Groups	Dose	% Increase in paw volume at different time interval after carrageen an injection					
		After 1 h	% change	After 3 h	% change	After 5 h	% change
Control	Q.S.	34.84 ± 4.27	--	78.54 ± 6.93		80.84 ± 7.75	--
Chitraka Haritaki Avaleha	1.8 gms/kg (360 mg/200gms)	22.33 ± 5.61	35.91↓	68.71 ± 7.67	12.51↓	64.99 ± 8.57	19.61↓
Shikhari Taila	4.32 ml/kg (0.864ml/ 200 gms)	29.612 ± 8.62 mine	15.01 ↓	83.88 ± 7.75	6.80	78.93 ± 8.06	2.36 ↓

Data: Mean ± SEM

***p> 0.01 in comparison to control group (Unpaired "t" test).

**P> 0.02. in comparison to control group (Unpaired "t" test).

Analysis from the above data reveals that *Chitraka Haritaki Avaleha* produced marked decrease (35.91%) in inflammation after one hour after carrageenan in comparison to control group. Shikhari Taila produced mild decrease (15.01%) in inflammation after one hour. Further *Chitraka Haritaki Avaleha* also produced mild decrease in inflammation after three hour (12.51%) and five hours (19.61%) of carrageenan in comparison to control group.

b) Antihistaminic Activity

i. *Effect of test drug on the Guinea pig ileum (in vitro)*

At the dose of 200 µg/ml of bath fluid were effective in inhibiting histamine (0.32µg/ml bath fluid) induced contraction of guinea pig ilium. *Shikhari Taila* produced almost 58% inhibition while *Chitraka Haritaki Avaleha* produced almost 32% inhibition of histamine induced ileum contraction. The kymographic recordings are provided in Fig- 01.

c) Compliance with Ethical standards

- *Funding:* This study was funded by Ministry of AYUSH. Grant in aid general of non- planned regular grant of IPGT & RA was provided for the present study.
- *Conflict of interest:* None.
- *Ethical approval:* The experiment was carried out after obtaining permission from institutional animal ethics committee vide permission (IAEC/15/2013/ 38) as per CPCSEA guidelines. The dose for the experimental study was converted based on the body surface area ratio by referring table of Paget and Barnes (1969).

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Development and Validation of an Instrument to Enhance the Community Pharmacy Practitioner's Knowledge towards Handling of High Risk/Alert Medications

By Balakeshwa Ramaiah M., Sejal Sharma, Saroj Poudel & Raju Koneri M.

Abstract- *Objective:* This study was aimed to prepare and validate an instrument as learning modules to boost community pharmacists' knowledge on high risk medications (HRM), which will help in minimizing serious consequences arising due to mishandling of HRM.

Methods: The instrument (videos) included chapters "introduction to HRM", "look alike and sound alike (LASA) drugs" and "storage and labeling of HRM". The instrument was ensured to be important, relevant, reactive and appropriate with the help of content and face validation which was then confirmed to be sensitive enough to distinguish knowledge levels of community pharmacists. The split-half reliability test by Kuder-Richardson formula 20 (KR 20) to obtain a homogenous reliability index value ($r_{KR20} = (k/k-1)/(1-\sum pq/\sigma^2)$), ensured internal consistency of the instrument.

Keywords: *high risk medications, community pharmacists, learning modules, content and face validation, reliability.*

GJMR-B Classification: *NLMC Code: QV 701*



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Development and Validation of an Instrument to Enhance the Community Pharmacy Practitioner's Knowledge towards Handling of High Risk/Alert Medications

Balakeshwa Ramaiah M. [α], Sejal Sharma [σ], Saroj Poudel [ρ] & Raju Koneri M. [ω]

Abstract- Objective: This study was aimed to prepare and validate an instrument as learning modules to boost community pharmacists' knowledge on high risk medications (HRM), which will help in minimizing serious consequences arising due to mishandling of HRM.

Methods: The instrument (videos) included chapters "introduction to HRM", "look alike and sound alike (LASA) drugs" and "storage and labeling of HRM". The instrument was ensured to be important, relevant, reactive and appropriate with the help of content and face validation which was then confirmed to be sensitive enough to distinguish knowledge levels of community pharmacists. The split-half reliability test by Kuder-Richardson formula 20 (KR 20) to obtain a homogenous reliability index value ($r_{KR20} = (k/k-1)/(1-\sum pq/\sigma^2)$), ensured internal consistency of the instrument.

Results: The five point likert scale showed an average score of above four points with content validity index (CVI) for I-CVI as 0.913 and for S-CVI as 0.916 was obtained. This indicated appropriateness, conciseness and importance of the training materials. The approval of the design of the learning modules was strongly highlighted when face validation was performed and the importance of the issues to community pharmacy profession was thus emphasized. The KR 20 index values homogenously reached 0.937 for introduction, 0.8424 for LASA and 0.8195 for storage and labeling chapters, suggesting that the learning modules were reliable, operational, feasible and attractive.

Conclusion: The validated instrument considered as an important tool to improve the community pharmacist's knowledge and handling of HRM (s), thus contributing for better patient care.

Keywords: high risk medications, community pharmacists, learning modules, content and face validation, reliability.

I. Introduction

Medications play a vital role in the management of diseases and its prevention. Medications are manufactured and marketed with potential of a wide range of safety. However, a rare class or group of medications, called as high risk or high alert medications (HRM), are known to have a risk in causing significant patient harm, disability or death if they are unintentionally misused or improperly administered. The term "high-risk" medications was initially coined by the Institute for Safe Medication Practices (ISMP) in 1998 for those drugs which are linked or related to most dangerous preventable adverse drug events (PADEs). Medication errors may not occur more often with high risk drugs but the consequences or impacts from them could be more dangerous for the patients. Therefore, various risks or hampers that could take place while prescribing, storing, dispensing, and finally administering a high risk drug should be carefully overseen at each phase of the medication management process.[1-3]

According to the American Pharmaceutical Association, eight categories were listed as high-risk medications that include high concentration electrolytes, chemotherapeutic agents, opiates, anticoagulants, narcotics, neuromuscular blocking agents, benzodiazepines and cardiovascular drugs. The process of drug dispensing or administration to patients at a hospital involves multifarious phases that in turn is based on a series of inter related actions and decisions overcoming daily obstacles. Nonetheless, this management process may not be satisfactorily safe every time, due to which the faults arising may or may not cause damage to the patient. These faults or mistakes, typically said as medication errors, arising in the administration pathway can be considered as preventable adverse events.[4] In 2003, ISMP performed a study for assessment of knowledge on high risk medications for distinguishing variances between pharmacy and nursing perspectives, most of the participants responded their agreement on which medications were considered high risk. This survey was repeated by ISMP in 2007 and 2012. In all the three surveys, it was noted that the pharmacists were not able to identify medications as high risk, as often as nurses did.

Author α ω: Pharm, PhD, Department of Pharmacy Practice, Karnataka College of Pharmacy, Bengaluru, India.
e-mail: balupharmacy@gmail.com
Author σ ρ: Pharm D, Department of Pharmacy Practice, Karnataka College of Pharmacy, Bengaluru, India.

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It is projected that a hospitalized patient is identified to be exposed to at least one error per day related to drug. According to ISMP, an estimate of as low as 450,000 medication errors result in injury to patients in the United States per year, with around 25 % of these errors meant to be avoidable. In addition, 7,000 deaths each year are recognized to be because of medication errors. In the field of community pharmacy, a few studies have been found to report the occurrence of injury to the patient caused by medication errors that are preventable. Ghandi TK and colleagues (2003)[5] mentioned that adverse events that were preventable occurred in 5% of ambulatory patients with medications that were dispensed from community pharmacies. Also, Gurwitz JH and colleagues (2000) [6] identified that one-half of life-threatening, serious or fatal adverse drug events resulted from medications dispensed from pharmacies that were preventable.

The study was thus aimed to prepare and develop instruments prior in labeling, handling, storage and dispensing of HRM for the pharmacists who would be further implemented with the important process of validation and reliability. As documented in several studies, validation has always been an important factor as the measurement of accuracy and consistency in research instruments. However, in various health and social science research taking place in developing countries, validation of instruments is not being commonly performed. This has been linked to the shortage of information on how validation should be carried out to certain degree of conclusion. As per a review article from a Nigerian researcher Bolarinwa OA (2015)[7], highlighted that the literary and technical meanings of instruments were both reflected by validation and reliability making them an important procedures to be done in research works. They elaborated numerous forms and methods of analyzing validation and reliability of an instrument, the main goal of which was to improve knowledge of these tests among young researchers in developing countries.[8,9]

According to an international literature published by Sampaio F and colleagues (2014)[10], an instrument that was proven to be valid and reliable was developed for assessment of knowledge in nurses regarding HRM. The validity consisted of content, construct and face validity whereas the reliability of the instrument was measured through internal consistency using Kuder-Richardson reliability 20 (KR 20) formula. In the same manner, considering the importance of assessment of knowledge of HRM to the community pharmacist, in this research, the instrument as educative materials, has been developed and validated by deep and vigorous study from various experts. Finally, the same was done with measurement of reliability with KR 20 for its internal consistency. This study was aimed to prepare and validate an instrument as learning modules to boost community pharmacists' knowledge on high risk medications (HRM), which will help in minimizing serious consequences arising due to mishandling of HRM.

II. Methods

The study was a prospective interventional methodological program. This study attempted on methods of preparation of an instrument in the form of suitable educative video materials, following with organization and analysis of data collected for the main purpose of validation of the research instruments and techniques. The summarized study methodology is represented in Figure 1.

a) Preparation and development of an instrument

For collection of data, the setting of HRM management in the particular area was needed to be known. So, a visit was made to various pharmacies for the same. With the respect to Indian pharmacy practice environment, training materials were suitably prepared on the information from global guidelines and practice for HRM management. Three informative and revealing chapters on management of HRM were prepared from various sources and literatures. The materials were prepared in such a way that they become easily understandable and comprehensive. The materials were both accessible in high resolution PC formats and size compressed mobile formats such that the acceptability of the material by the participants would highly be favored. It was reaffirmed that the training materials would be helpful as a knowledge material in the Indian setup. The training material in the form of hard copy was validated (already accomplished) out of the objective of the study. After which, the hard copy materials were converted to scripts in the form of narrations for the purpose of recording it and preparing as convenient video materials. The language of the script was ascertained for easy understandability.

b) Development of an instrument in the form of video materials

A suitable female artist was chosen for the recording the script; considering factors like voice, tone, clarity of pronunciation, speech flow and finally delivery of the speech. The whole process was carried out in a studio environment under the supervision of a technical team having hands-on experience in recording and editing such videos. The processing of the video materials involved the following five crucial steps viz (i) Recording the scripts using appropriate voice software into individual sound tracks and then joining up the same into one single audio file. (ii) Collaborating the slides of power point presentations with their specific audio files to produce a video file. (iii) Adjustment of time intervals. (iv) Addition of suitable background tracks to the collaborated file. (v) Converting the file into

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high resolution PC format as well as in compressed mobile format. The software such as Audio Recorder by Green Apple Studio.[Version 1.9.45], Audacity. The free, Cross- Platform Sound editor by Audacity Development Team. [Version 2.1.3] and Corel Video Studio Ultimate X1 was utilized for the purpose of recording the scripts and collaborating it with the slides of the power point materials. The videos were finally ensured to be checked for synchronization and clarity.

c) Validation of the Instrument

Various literature evidences implicated the importance of the validation as a degree to which a measurement measures what it purports to measure. A validation technique can be either logical or rational. Validation illustrates the estimate of how much a measure or a dimension represents each and every single component of a hypothesis. The content validity (8 experts involving senior consultants and community pharmacist) and face validity (45 community pharmacy practitioners) were performed in this study. The prepared instrument (Learning modules) was ensured to be important, relevant, reactive and appropriate with the help of content and face validation and was then confirmed to be sensitive enough to distinguish knowledge levels of community pharmacists.

A total of 45 pharmacists (15 hospital pharmacists and 30 community pharmacists) were involved for the process of reliability. For the collection of data from the participant's responses regarding the training material, a form containing scoring columns for various aspects related to the material such as contents, clarity of the video and audio as well as various diagrammatic illustrations was distributed. The final scoring and feedbacks were evaluated and the appropriateness and reliability of the material was finally measured with KR 20.

i. *Content Validity*

The percentage of agreement among specialists as to the instrument assessment and its item was obtained by means of the calculation of content validity index (CVI). This index permits for the analysis of each item individually, and subsequently, the instrument as a whole. Lynn MR (1986)[11] through rigorous research illustrated that the researchers follow CVIs of two types based on the agreement of experts on the content of the instrument. It involves the Item-Content Validity Index (I-CVI) and Scale level- Content Validity Index (S-CVI). For I-CVI, the settlement among reviewers concerning each item of the instrument was measured by means of a Likert scale, with scores that range from score 1 to 4 (where, 1=irrelevant, 2=slightly relevant, 3=fairly relevant and 4=extremely relevant) Item that obtained scores of 1 or 2 were reviewed or eliminated. The calculation of the I CVI for each item consisted of the division between the numbers of answers that were fairly and extremely relevant by the total number of answers. The study also recommended an I-CVI > 0.78 for analyses of instrument by six or more judges.

The S-CVI involves the mean proportion of items rated as fairly and extremely relevant across various experts. This description of the CVI for scales was referred as S-CVI/average as for the purpose of convenience. This was interpreted as the combination of the number of items that were rated fairly and extremely relevant by all experts and to then which the total number of all the ratings is divided. It is also theorized that the S-CVI/ average is the mean or average I-CVI value because it happens to concentrate on mean or average item quality rather than on average enactment by the experts.[12,13] Waltz CF and colleagues (2005) [14] stated that for mean congruity, the standard value to be considered is 0.90.

ii. *Face validity*

Face validation consists of the subject experts observing thoroughly at the items in the instrument (learning modules) and approving that the test is a valid measure of the conception which is being evaluated just on the face of it. In simple words, they are assessing each aspect of the measuring items if they really match with the theoretical domain of the model. The approval of the design of the learning modules was strongly highlighted when face validation was performed and the importance of the issues to community pharmacy profession was thus emphasized as the experts understood all the components of the training material providing them with a secure atmosphere.

iii. *Reliability*

The demand of reliability for measurement of internal consistency of a test is that it is needed to be estimated after only one test administration which therefore helps to escape the issues associated with testing over multiple time periods. By KR-20 formula, an index score for reliability was calculated as shown in the Formula 1.

$$r_{KR\,20} = \left(\frac{k}{k-1}\right)\left(1 - \frac{\sum pq}{\sigma^2}\right) \quad (1)$$

Where, $r_{KR\,20}$ is the Kuder-Richardson formula 20; k is the total number of test items$\sum$ indicates to sum; p is the proportion of the test takers who pass an item; q is the proportion of test takers who fail an item; σ^2 is the variation of the entire test.

III. Results

As illustrated in Table 1, the mean I-CVI was figured out to be 0.913. Lynn MR (1986)[11] also suggested that when there is participation of five or fewer experts, there should be a universal agreement on the content validity for their rating to be said as an equitable representation. As per definition, the

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S- CVI/average is the combination of number of items rated either extremely or fairly relevant by all experts (Y), divided by the total number of all the possible ratings. Therefore, the S-CVI/ average was found to be 0.916 (Table 1). The overall reliability for all three chapters are shown in Table 2. In this study the overall sample observations used for the reliability (n= 45) was documented in excel sheet and the correct score per slide for the respective chapters was obtained as shown in Tables 3, 4 and 5 respectively. The mean sum of product of proportion passed and proportion failed was calculated to apply standard deviation for each individual slide of all the three chapters and finally KR-20 reliability formulae was applied. The individual chapters were considered for their reliability, from which the index was obtained as 0.937, 0.8424 and 0.8195 for chapter 1, chapter 2 and chapter 3 respectively.

IV. Discussion

a) Content Validity

The content validity index was reported only in methodological studies because it has focus only for explaining the process of content validations.

i. *Item-level content validity Index (I-CVI)*

I-CVI is used commonly by researchers to obtain information on guiding themselves in reviewing, erasing, or replacing items. However, the researchers do not generally provide information about I-CVI values in their reports, as I-CVIs are meant only to be reported in procedural research which mainly concentrates on clarifications of the overall content validity process. I-CVI is calculated as the total number of experts giving a fair or extreme rating of either 3 or 4 (thus dichotomizing the normal scale into either relevant or not relevant), divided by the total number of experts. In simple words, the I-CVI should be exactly 1.00 when there are five or fewer experts giving their ratings. The standard value could be a little relaxed when there are six or more raters, but I-CVIs should not be lower than 0.78. For example, there could be one ''not relevant'' rating (I-CVI ¼ i.e. 0.83) with six raters and there could be two not relevant ratings with nine raters. Thus, the mean I-CVI which we obtained could be considered as an ideal value.

ii. *Scale-level content validity Index (S-CVI)*

The S-CVI/ average is constantly identical to the average congruency percentage (ACP). Rubio D and colleagues (2003)[15] demonstrated their content validity procedure, while evolving the Caregiver Well-Being Scale, in which they used the averaging approach for the S-CVI based on ratings of relevance by six judges. This method for the calculation of S-CVI was approached in particular with a concern that while performing universal approach with more than 6 raters the content validity index would be slightly depressed, because universal approach demands agreement among all experts. Similarly, Waltz and colleagues (2005)[14] stated a recommendation on the standard value for the acceptability of S-CVI as 0.90 but not 0.80.

b) Reliability

While instituting the quality of a settled instrument wholly, Kuder and Richardson developed a formula known as KR-20. In estimating the reliability of a test based on internal consistency, also called as reliability coefficient, KR-20 has been the most widely used formula. It requires only a single administration of a test. The internal consistency by KR-20 is obtained by evaluating the consistency of the material within a test based on the total number of items in the test as a whole, the proportion of participants giving correct answers for each item and the standard deviation of total score obtained. The value could range from 0 to 1. The closer the score is to 1, the more reliable the test. A study[16] stated when KR-20 formula is in use, the internal consistency estimates ranges from 0.75 as an acceptable mark to an excellent 0.97 mark.[12]

A KR20 value range of 0.86 to 0.94 was reported by Lin and colleagues (1999)[17], for the analysis of internal consistency while doing item analysis of a multiple choice test questionnaire which was then used in licensure examination for registered nurses. Also, Sampaio F and colleagues (2014)[10], used KR reliability for their true and false tests in development of valid instrument to assess nurses' knowledge of High risk medication in a tertiary care hospital, and got a value of 0.74, which indicated acceptable reliability. While, Priscila P and colleagues (2015) [18] did the Brazilian transformation of the work done by Taiwanese researchers [10], where they too computed KR 20 formulae for their instrument to assess nurses' knowledge and obtained a value of 0.74 respectively. Similarly, Farhan B (2018)[19] designed an instrument for students to observe tests involved in the research of a string ensemble course for music students and while examining its reliability, they used KR 20 formula, therefore the value of which was obtained as 0.717. Also, a study[20] developed an Instructor-Mediated Performance Assessment Test, for which they did reliability and obtained an index of 0.95.

V. Conclusion

This study was an effort to prepare suitable informative materials in the form of videos that would benefit community pharmacists on their perspective about HRM and its management. The insufficiency of basic knowledge on this topic in the Indian setting of community pharmacy was highly reflected when pharmacists were evaluated previously with a set of questionnaire regarding various aspects of HRM management, out of the objective. With this concern, instrument in the form of learning modules consisting of

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demanding information on various aspects of high risk medication management was prepared and finally validated. The validation done by content validity received an I-CVI of 0.913 and S-CVI of 0.916, which were considered as ideal values. Similarly, reliability followed with KR 20 formula analysis. The reliability index was obtained as 0.937, 0.8424 and 0.8195 for chapter 1, chapter 2 and chapter 3 as parts of the learning modules. The prepared instrument thus can be concluded as valid and reliable source to benefit community pharmacists for management of HRM and finally for better patient care.

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Table 1: Content Validation by six experts using content validity index

Chapters	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Expert 6	Expert 7	Expert 8	Number in Agreement	Item CVI (I- CVI)
Introduction to HRM	Y	Y	Y	Y	Y	Y	Y	N	7	0.87
LASA	N	Y	Y	Y	Y	Y	Y	Y	7	0.87
Storage and labelling	Y	Y	Y	Y	Y	Y	Y	Y	8	1.00
Mean I-CVI= 0.913 Mean S-CVI= 0.916										
*I-CVI = Item-level content validity index. *S-CVI = Average scale- level content validity *Y = Agreement on the content by the expert, *N = Disagreement on the content by the expert										

Table 2: Representation of index value and reliability for the three learning video modules

Chapter No.	Chapter Name	Index	Reliability
1.	Introduction to High risk medications	0.937*	Homogenous
2.	Look-alike and sound-alike medications	0.8424*	Homogenous
3.	Storage and labelling	0.8195*	Homogenous

*if the index value is >0.50 the sample is having good reliability

Table 3: Reliability table for the chapter "Introduction of HRM" by KR 20 Formula

Slide Number	Correct Score	Proportion Passed	Proportion Failed	p*q
1	26	0.57	0.43	0.245
2	32	0.7	0.3	0.21
3	26	0.57	0.43	0.24
4	31	0.68	0.32	0.2176
5	15	0.33	0.77	0.2541
6	30	0.66	0.34	0.2244
7	21	0.46	0.54	0.2484
8	11	0.24	0.76	0.1824
9	23	0.51	0.49	0.2499
10	25	0.55	0.45	0.2475
11	27	0.6	0.4	0.24
12	30	0.66	0.34	0.2244
13	29	0.64	0.36	0.2304
14	36	0.8	0.2	0.16
15	15	0.33	0.77	0.2541
16	35	0.77	0.33	0.2541
17	30	0.66	0.44	0.4224
18	25	0.55	0.45	0.2475
19	28	0.62	0.38	0.2356
20	30	0.66	0.34	0.2244
Mean Sum of p*q: 5.0663; Standard deviation squared: 46.0648 Index value $\mathbf{r_{KR20}} = \left(\frac{k}{k-1}\right)\left(1 - \frac{\sum pq}{\sigma^2}\right)$: 0.937				

Table 4: Reliability table for the chapter "Look-alike and sound-alike medications" by KR 20 Formula

Slide Number	Correct Score	Proportion Passed	Proportion Failed	p*q
1	35	0.77	0.33	0.2541
2	32	0.71	0.29	0.2059
3	33	0.73	0.27	0.1971
4	34	0.75	0.25	0.1875
5	26	0.57	0.43	0.2451
6	29	0.64	0.36	0.2304
7	24	0.53	0.47	0.2491
8	35	0.77	0.33	0.2541
9	32	0.71	0.29	0.2059
10	33	0.73	0.27	0.1971
11	34	0.75	0.25	0.1875
12	28	0.62	0.38	0.2356
13	22	0.48	0.52	0.2496
14	29	0.64	0.36	0.2304
15	26	0.57	0.43	0.2451
16	29	0.64	0.36	0.2304
17	33	0.73	0.27	0.1971

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18	19	0.42	0.58	0.2436
19	20	0.44	0.56	0.2464
20	22	0.48	0.52	0.2496
21	29	0.64	0.36	0.2304
Mean Sum of p*q: 4.8962; Standard deviation squared: 21.8146 Index value $\mathbf{r_{KR20}} = \left(\frac{k}{k-1}\right)\left(1 - \frac{\sum pq}{\sigma^2}\right)$: 0.8424				

Table 5: Reliability table for chapter "Storage and labelling" by KR 20 Formula

Slide Number	Correct Score	Proportion Passed	Proportion Failed	p*q
1	27	0.6	0.4	0.24
2	25	0.55	0.45	0.2475
3	23	0.51	0.49	0.2499
4	30	0.66	0.34	0.2244
5	24	0.53	0.47	0.2491
6	28	0.62	0.38	0.2356
7	34	0.75	0.25	0.1875
8	36	0.8	0.2	0.16
9	33	0.73	0.27	0.1971
10	30	0.66	0.34	0.2244
11	30	0.66	0.34	0.2244
12	31	0.68	0.32	0.2176
13	34	0.75	0.25	0.1875
14	34	0.75	0.25	0.1875
15	33	0.73	0.27	0.1971
16	30	0.66	0.34	0.2304
17	30	0.66	0.34	0.2304
18	31	0.68	0.32	0.2172
19	24	0.53	0.47	0.2491
20	34	0.75	0.25	0.1875
Mean Sum of p*q: 4.3442; Standard deviation squared: 19.6144 Index value $\mathbf{r_{KR20}} = \left(\frac{k}{k-1}\right)\left(1 - \frac{\sum pq}{\sigma^2}\right)$: 0.8195				

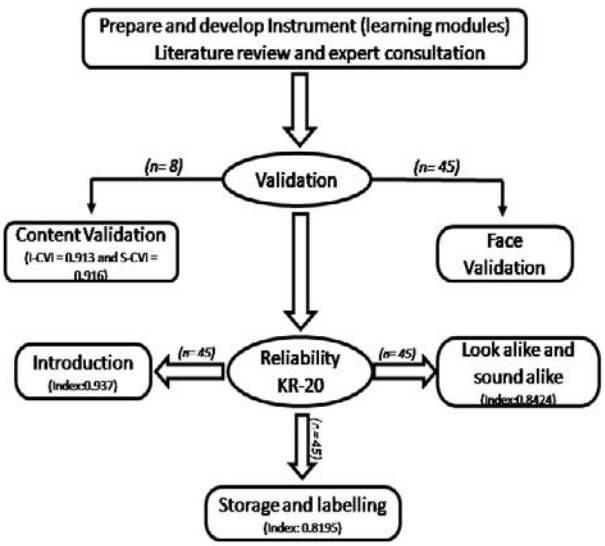


Figure 1: The overall study procedure along with reliability scores

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Doha Declaration: Compulsory Licensing and Access to Drugs

By Ms. Kiran Kumari & Dr. Ajay Sharma

Mewar University

Abstract- This paper analyses compulsory licensing evolution phases and sheds light on reasons behind development especially after trade related aspects of intellectual property rights (TRIPS) provisions. Without patents, the innovators can neither be adequately compensated for their costs of research nor be encouraged for further research to develop new and improved products. Patent protection is therefore accepted as a necessary evil, despite its conflict with the competitions laws and human rights law (in case of pharmaceutical patents). Prior to Doha declaration pharmaceutical companies were enjoying the monopoly right because of patent protection regime for manufacturing, sale, and import the products which result into high cost of the patented products. Doha Conference on November 14, 2001 forced many countries to amend their patent rights for the purpose of compulsory licensing. This increased cost on patented molecules was a major hindrance for access to medicine. Public health officials considered Doha Declaration on compulsory licensing a positive approach in prioritizing public health over intellectual property rights. (Jain, 2009)

Keywords: *TRIPS, compulsory license, patent.*

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Doha Declaration: Compulsory Licensing and Access to Drugs

Ms. Kiran Kumari [α] & Dr. Ajay Sharma [σ]

Abstract- This paper analyses compulsory licensing evolution phases and sheds light on reasons behind development especially after trade related aspects of intellectual property rights (TRIPS) provisions. Without patents, the innovators can neither be adequately compensated for their costs of research nor be encouraged for further research to develop new and improved products. Patent protection is therefore accepted as a necessary evil, despite its conflict with the competitions laws and human rights law (in case of pharmaceutical patents). Prior to Doha declaration pharmaceutical companies were enjoying the monopoly right because of patent protection regime for manufacturing, sale, and import the products which result into high cost of the patented products. Doha Conference on November 14, 2001 forced many countries to amend their patent rights for the purpose of compulsory licensing. This increased cost on patented molecules was a major hindrance for access to medicine. Public health officials considered Doha Declaration on compulsory licensing a positive approach in prioritizing public health over intellectual property rights. (Jain, 2009)

Keywords: TRIPS, compulsory license, patent.

I. Introduction

Exclusive rights on innovations is permitted to an individual known as patent holder for twenty years who invents a useful or something new products or process. Patent holder enjoys a kind monopoly right which prevent him from exploitation on inventions. Government provides rewards in the form of royalty to the patent holder on efforts and skills which encourage further research and innovations. (Gupta, 2010) Research and development in pharmaceutical is very costly affair, unpredictable in nature and also time consuming process. Therefore patent on intellectual property rights to the innovator pharmaceutical firm is must, which may prevent patent abuse and allows competitor to enter into generic medicine market. (Kaur et al., 2015)

Research and development in pharmaceutical patents provides patent holder a kind of monopoly rights. If patent holder is not compensated adequately for cost on research and development activity incurred on development of a new product leads to decline in research and development activity. Patent holder is compensated in the form of royalty for innovations on on patent by government for use of innovation in case of compulsory licence without permission from holder of patent. (Durojaye, 2011)

"It is necessary to strengthen the system of compulsory licenses in the developing and least developed countries because of their inability/ inefficiency to cater to the needs of its people. And the granting of compulsory licensing over the patent protected drugs shall give monetary benefits to the patented pharmaceutical companies". Unites State criticized the implementation of compulsory licensing provisions because compulsory licensing policy reduces the benefits of further research and development. An individual under intellectual contribution on any research and development activity must enjoy the patent exclusive right. Monopoly right which is provided to the inventor has both the implications with regards to human rights law as well to the competition laws. Thus an effective mechanism is necessary to ensure the fair usage of the exclusive monopoly rights and compulsory licensing is one such safeguard. And granting of compulsory licenses to the developing countries on one hand can be least expensive and beneficiary to the people who are in need but at the same time it can incur heavy loss or put burden on the companies creating it but if it is seen from another point of view then it can be said that granting of compulsory licenses by paying the royalty to the originator company can make money to them which they would not be able to make it in the potential market due to the high prices. This review paper will deal with the issues related to that and analyse the aspects where granting of compulsory license can be beneficiary to the inventors in cases of pharmaceutical companies.

II. Research Objectives

1. To highlight the Doha Declaration and examine the relationship between the access to drugs and the employment of compulsory licensing.
2. To outline the Compulsory License regime in India and to ascertain the rationale and impact of the Judgment given by Supreme Court to Bayer Corporation v. Union of India.
3. To trace out whether the compulsory licenses for patent protected drugs is a necessary measure, or a threat to innovation.
4. To draw conclusions towards grant of compulsory licenses.

Author α: Research Scholar, Mewar University Chittorgarh Rajasthan. e-mail: Kiranleo47@rediffmail.com
Author σ: Assistant Professor, T.I.T. & S Engineering College Bhiwani Haryana. e-mail: ajaysharmapuru@rediffmail.com

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Lord Macaulay law commission recommendations in 1856 first legislation came on patent.

Some important development of the patent regime is given below:

- Indian Patents and Design Act 1911. (Act II of 1911).
- Lahore High Court retired Judge Report 1950(Tek Chand Committee). This Committee Report 1950 led to the passing of The Indian Patents and Designs (Amendment) Act 1950.
- (Act No XXXII of 1950).
- Justice Rajagopala Ayyangar Committee Report 1959 on retention of Patent System. (Ayyangar, 1959).
- The Patents (Amendment) Act 1999. (Act 17 of the Patents (Amendment) Act 1999).
- The Patents (Amendment) Act 2002. (Act 38 of 2002. The Patents (Amendment) Act 2002).
- The Patents (Amendment) Bill 2003. (Bill No 92 of 2003 Lok Sabha)
- The Patents (Amendment) Act 2004. (Order No 7 of 2004 TRIPS compliance by 2005).
- The Patents Act 2005 amended. (The Patents Amendment Act 2005).

III. What is a Compulsory License?

Compulsory licenses means license given by Government for manufacturing, use and sell a particular drug or for the use of a particular process to a third-party which has been invented and patented without permission from patent holder.

a) Compulsory license origin in india

After Independence Indian Government realized the need for the patent regime. Government of India formulated Tek Chand Committee towards the end of 1948, the committee known as Bakshi Report 1950, to check the pre existing Indian patent legislation for patent regime betterment. In year 1999 amendment was done first time in Indian Patent Act 1970, next amendment was done in year 2002 and 2005 subsequently. The third amendment in Indian patent act 1970 explored the development of voluntary licensing and change for the grant of voluntary license that are contained within the section 84 - 92 of the Indian Patents Act 1970. Grounds for getting permission on Compulsory license is by writing an application under section 84 (1) to the patent controller after expiry of patent period which shall be three years from the date of the sealing of innovation on patent on the following grounds:

1. If affordable necessities of general public have not been fulfilled,
2. If innovation on patent is not worked within the territory of India,
3. If the patent invention is not accessible to the general public at an economic price.

b) Access to medicines and compulsory licensing

Though the TRIPS Agreement was proposed to address intellectual property rights as a trade related issue, the enforcement of the rule had sweeping connotations beyond the terms in which they were negotiated and adopted. Most of the developed countries developing countries under TRIPS excluded pharmaceutical products from patent protection. For example, Brazilian legislation amendment in 1969 declared pharmaceutical processes and products non-patentable. India implemented process patent in year 1970, for pharmaceuticals which result into the development of a strong local pharmaceutical sector. Most of the countries feared that product patenting of pharmaceutical drugs would result in endangering affordability to general public. Moreover, the rationale of such a policy is to give space for the local industry to manufacture pharmaceutical product easily and without infringing. As said, the TRIPS obligate patent protection to pharmaceuticals. The monopoly granted to pharmaceutical industry resulted in high prices for medicines. In result, the right to the exclusive use of protected drugs excluding potential competition conflicted with the fundamental right to health, one more manifestation of which is the access to medicines needed by all. (Ford & Sara., 2000)

IV. Cases of Pharmaceutical Firms

1. Novartis AG Pharmaceutical Company failed to win patent protection on medicine named Glivec whose application was rejected by Supreme Court of India. Many healthcare activists opinioned to Government for providing economic medicine, as branded or patented medicine are too costly to afford for poor people of the country. A report given by Novartis AG Pharmaceutical Company on economic medicines was that around sixteen thousand patients use medicine named Glivec and most of them received these medicines as free of cost. In the United State Pharmaceutical Industry trade group in research said that this compulsory licensing policy decisions are deteriorating environment for further research and innovations.

"*Protecting intellectual property is fundamental to the discovery of new medicines," the group said in a statement. "To solve the real health challenges of India's patients, it is critically important that India promote a policy environment that supports continued research and development of new medicines*."

This legal battle for compulsory licensing started when Supreme Court's denied for compulsory licensing in case of Pharmaceutical firm Novartis AG for a patent of drug named Glivec in 2006. (Kulkarni et al. 2013).The Battle for Compulsory license on patent regime was started in years 2006 and ended in year 2013 by the decision of Supreme Court in India. Novartis

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AG Pharmaceutical Company medicine named Glivec generic version of drug was the leading case for amendment in the Patent Act 1970 for Compulsory license on patent regime which forced Indian government to rethink over intellectual property rights on patent related issues. Novartis AG Pharmaceutical Company's product named Glivec generic version of drug failed in the tests of R&D, inventions under The Patent Act. However Novartis AG generic version medicine Glivec was granted patent in U.S, China and Russia, but was unable to fulfill the requirement of patentability of Indian Patent Act.

"*Indian Patent Act 1970's Section 3(d) deals in the discovery of any new property of new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant and Section 3(b) (an invention the primary or intended use of which would be contrary to law or morality or injurious to public health)".* These two sections 3(d) & 3(b) were the hurdle in Novartis AG Pharmaceutical Company's product named Glivec for which they did not received patent. (Ahmed, Taylor & Kumar, 2012 & 2013)

Jurisdictional analysis

1. *India*

Indian Patent Office has issued first compulsory license in year 2012 to pharmaceutical company named Bayer Corporation for innovation on cancer drug name sorafenib tosylate (Nexavar), which authorize NATCO a domestic generic medicine producer which also produce a low-cost version of the drug for two reasons mentioned below:

a) "Production of generic version of medicine by NATCO a domestic generic company over Bayer Corporation named Nexavar that would be cost effective than the patented medicine and thus reducing monopoly over the drug in the Indian market."

b) "It may give an opportunity to other Indian generic drug manufacturer, if the innovator pharmaceuticals fail to supply patented medicine in large quantities at affordable prices."

2. *Case of Natco vs. Bayer. (Chaudhuri, 2002)*

- Bayer Corporation invented the drug Sorafenib in year 1990.
- Bayer Corporation in the United States applied for a drug patent in year 1999.
- Bayer Corporation launched the medicine under the brand name Nexavar in the market year 2005.
- Bayer Corporation received a patent for the drug in India year 2008.
- Indian drug Manufacturer Company named Cipla pharmaceuticals started selling of a generic version of Nexavar in year 2010.
- Generic manufacturer pharmaceutical firm based in Hyderabad named Natco pharmaceutical applied for a voluntary licensing to the patent controller of India for manufacturing generic version medicine under the name of Nexavar year 2011.

3. *Lee Pharma Limited vs. Lee Pharmaceuticals*

"*In June 2015, Lee Pharma filed an application for seeking the grant of a compulsory licence for manufacturing and selling the drug Saxagliptin used in the treatment of type-II diabetes mellitus. Saxagliptin is patented by Bristol Myers Squibb and marketed by AstraZeneca in India. The Controller rejected the application mentioning that applicant failed to satisfy regarding any of the grounds as specified in the section 84(1) of the Act*". (Lee Pharma Limited vs. Lee Pharmaceuticals on 8 May, 2017)

V. Grant of Compulsory License under Section 84 due to Unaffordable Prices and non Working of Patented Article

Compulsory licensing are granted as following conditions

1) Prevent the patent abuse as a monopoly.
2) Commercial use of the patented inventions by an interested person.
3) Address the access of public health concern in India.

VI. First Compulsory Licensing of Patent in India

First compulsory license was given to Natco Pharma Ltd. on 9 March 2012 by the patent office to manufacture generic version of Bayer Corporations medicines named Naxavar which is used in treatment of kidney and liver cancer. (The Intellectual Property Appellate Board)

VII. Indian Patents act 1970's Main Features

1. Patent Act 1970 fills the gap between the patent holder rights towards society and his obligations.
2. Section 83 curbed the monopoly rights of patent holder. Patents are granted to encourage inventions not to enjoy monopoly rights and to accelerate domestic industrial growth.
3. The Act allows process patents in food, medicines substances and drugs by chemical processes as health and food are important factors.
4. Patents Act 1970 under Section 53 provides protection of patent innovations up to a period of 14 years and in case of medicine it is provided for 7 years. This shorter period help the society just in case of monopoly as patentee may charge higher price.

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VIII. Provisions of Intellectual Property Rights

1. Article 27.1 enlarge the scope of product or Processpatent and also protects patent holder from discrimination on the basis of inventions, production and technology.
2. Article 33 extends patent protection period up to twenty years.
3. Under Article 31 limited compulsory licenses scope, government and for third party use. (Rana, 2018)

IX. Grounds for Compulsory License Issue

Compulsory License would be issued under following circumstances:

1) *Bayer Corporations Ltd failed to meet the general public need with reference to the patent invention and at the reasonably affordable price.*

Bayer Corporations Ltd. failed to fulfill the public requirements with regard to the drug access at the reasonably affordable price. Natco Company Ltd. on July 29, 2011. filed an application for issue of Compulsory License to the controller of patent in India for the manufacturing and sale of the generic version of patented medicine in India by its own brand name at price less than rupee ten thousand per month therapy against Bayer Corporations Ltd. who charged Rs.2, 80,428/- for one month therapy. The term affordable means general public purchasing power for the medicine. Division Bench of Bombay High Court held that of Pharmaceutical Company Bayer Corporations Ltd. did not adhere to the reasonably affordable price policy.

2) *Patented drug of Bayer Corporations Ltd (Nexavar) had not in the territory of India*

Under Article 27 of TRIPS: Bayer Corporations Ltd. argued that there can be no discrimination for the patented medicines, Manufactured or imported. Division Bench of Bombay High Court held that patent holder must perform some efforts for manufacturing of the drug in India. An argument made by Bayer Corporation Ltd. that the Compulsory license granted to Natco Pharmaceutical Company was against the conditions mentioned under Section 90. Adequate remuneration will be provided to the patent holder while granting voluntary license which is mentioned under TRIPS Agreement under Article No 31. Decision made on 9 March 2012 provided that 6 percent royalty was paid of total sales made paid by Natco Company Ltd. and reasons for fixing 6 percent royalty was that the petitioner failed to show the evidence for the cost incurred on inventions. Normal rate of royalty should be 4 percent as per United Nation Development Programme recommendations and by patent controller this royalty was again adjusted to 6 percent of the net sale. Further Tribunal has increased the royalty by 1 percent i.e. up to 7 percent of net sales made by Natco Company Ltd. The petitioner failed to show in what manner the royalty was fixed at 7 percent. (Chandiramani, 2002)

a) Indian and European Countries provisions on compulsory license

1. "Export of innovative pharmaceutical medicinal products under paragraph 6 decision in Doha Declaration deals under Section 92A in Indian and regulation No (EC) 816/2006 in Europe".
2. "Mandatory cross-licensing between the owners of patented biotechnology inventions and registered plant variety under Directive 98/44/EC provisions in the European regulations".
3. Provision in Indian Patents Act under section. 84 (1) (c) and Provision in China for Patents Act under Article 48 deals in Non-functional of the patent.
4. Provision in Indian Patents Act under Section 83 (f) and Provision in China for Patents Act under Article 48 deals in Anti-competitive practice by the patentee.
5. Provision in Indian Patents Act under Section 92 and Provision in China for Patents Act under Article 49 deals in Circumstances of national emergency or extreme urgency.
6. Provision in Indian Patents Act under Section 92 and Provision in China for Patents Act under Article 50 deals in Public health crises.
7. Provision in Indian Patents Act under Section 92 A and Provision in China for Patents Act under Article 50 deals in Export of patented drugs.
8. Provision in Indian Patents Act under Section 91 and Provision in China for Patents Act under Article 51 deals in Licensing of related patents.
9. Provision in Indian Patents Act under Section 90(1) (vii) and Provision in China for Patents Act under Article 53 deals in Predominant use for the domestic market
10. Provision in Indian Patents Act under Section 84 (6) (IV) and Provision in China for Patents Act under Article 54 deals in Prior efforts of the applicant to obtain a voluntary license is necessary.
11. Provision in Indian Patents Act under Section 94 and Provision in China for Patents Act under Article 55 deals in Termination of the compulsory license.
12. Provision in Indian Patents Act under Section 90 (1) (iv) and Provision in China for Patents Act under Article 56 deals in Non-exclusive basis
13. Provision in Indian Patents Act under Section 90 (1) (i) and Provision in China for Patents Act under Article 57 deals in adequate remuneration to the patentee.
14. Provision in Indian Patents Act under Section 117 A and Provision in China for Patents Act under "Article

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58 deals in Decision on compulsory license subject to judicial review". (Mathur et al., 2016)

b) *The salient features of compulsory licensing under the TRIPS Article 31 are:*

- "Article 31(a) deals in the application for the issue of compulsory license shall be considered on its individual merits basis".
- Permission on voluntary license lies in the prior efforts made by applicant from patent holder on the basis of commercial terms and conditions which may be waived in the case of a national emergency or in the cases of public non-commercial use.
- "Compulsory license shall be issued on non-exclusive basis given in Article 31(d)".
- "compulsory license shall be granted for the purpose of availability of medicines only in the domestic market of the country who will issue the license [Article 31(f)]";
- The holder of patent must get enough remuneration on the basis of expenditure made by him. [Article 31(h)];
- "The compulsory license shall be under legal validity and any decision related to license will be subject to judicial review in the country who issues the compulsory license [Article 31(i) and (j)]".
- Member of World Trade Organizations conference in Qatar on 14 November, 2001 adopted the "Declaration on the TRIPS Agreement and Public Health". (WTO Ministerial Conference Doha, 2001)

X. A Compulsory License may Additionally be Granted in the Following Ways

Section 92 A - "*In Exports, national emergencies of general public for uncommercialized use by proper notification to Central Government in the official gazette*".

Section 92 A (1) "*To the countries in which pharmaceutical sector having light or insufficient producing capacity to handle general public health related problem*".

Natco Pharma applied first for compulsory license in India for the producing Roche's innovation in the medicine named Erlotinib used in cancer and failed for export it to Nepal, then second application was made by Natco Pharma for the production of medicine named (Sutent) Sunitinib then again license was not again permitted.

On dated 9 March 2012, Natco received compulsory license for manufacturing Bayer's patented medicine named Nexaver in India by considering all the factors which were listed under section 84 of the Indian Patent Act 1970 on the grounds mentioned below:

1. Affordable necessities of general public have not been fulfilled,
2. Innovation on patent is not worked within the territory of India,
3. The accessibility on patent has not been fulfilled to the general public at an economic price.

Ministry of health in India on January 2013 allowed for production of generic medicine of the innovated firm i.e. three type's anti-cancer medicines namely dasatinib, trastuzumab, and Ixabepilone and selling them at an affordable price. (Chander et al., 2013)

XI. Advantages of Compulsory Licensing

1. Compulsory licensing breaks up monopolies and cartels agreements and sometimes provide their residents for access to life-saving drugs at an affordable price.
2. It helps in economic growth and technological advancement of the country.
3. It encourages research and development activity.
4. It is argued that compulsory licensing helps in developing a local generic pharmaceutical market. (Bayer Corporation vs. Union of India, 2014)

XII. Disadvantages or Consequences of Compulsory Licensing

Patented drug supplied into local market may create a kind of gray (illegal sale) market for many reasons. It is a situation when a drug is supplied into other market for which this policy was not designed and for sale on low prices than list price in the targeted market. (Christensen, 2012)

This kind of marketing strategy is the contravention of the (IPR) Intellectual property rights. Where compulsory license for manufacturing of generic medicines provided to produce and for selling the innovated drug to market and the firm or their dealers sell the medicines to other country may lead to the patent abuse, which is seen in the case of license given for import of medicines. These medicines are known as counterfeit medicines which impose a heavy loss on health of public and patent holder. So gray (illegal sale) market requires a tight check while granting compulsory license. Pharma company dealers and the manufacturers are some time responsible for grey marketing situations and to avoid this situation medicine batch must contain a punch line "only to be sold in particular country" and "only for export". For Instance in year 2002 medicine named Procrit for treating anemia in cancer was a counterfeit medicine because of using non sterile water which results into major infections. (Yadav, 2015)

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XIII. Perspective of Compulsory Licensing Globally

1. Increases in competition globally would result into reduction in prices due to which more generic companies would come into market to increase their share into market. So that patients can access economic medicines and compulsory licensing breaks up monopolies and cartels agreements sometimes and will save lives by ensuring accessibility of drugs at affordable prices.
2. Compulsory licensing will discourage research and development activity because it will make them dependent on the generic medicines because of low cost on investment as compare to cost on research and development activity.
3. Financially challenged patients: This development of compulsory licensing in developing countries would be useful for the poor patients for simple access and utilization to the medicines at low cost. Some pharmaceuticals gives free access to the medicines to the economically challenged people by launching programmes such as free access to the medicine within developing countries to shield their patent.
4. Development of compulsory licensing practiced completely different view across globe. Unavailability and unaffordability of the medicines in most developing countries are major issues for the grant of compulsory licensing policy. Opposite of this developed and underdeveloped countries putting pressure on developing countries like Europe and United State for non issuance of compulsory license as a reason that it would lower the research and development activity. China in year 2012 conjointly had opened the manner for generic version of medicines by creating a change in Intellectual property laws and this allowed china government to permit compulsory licenses for manufacturing generic version of medicines which would be economic to general public use. Zimbabwe in year 2003 issued its first compulsory license to Varichem Pharmaceutical Co. which is a local generic pharmaceutical firm to manufacture anti retroviral medicine for low income people. Compulsory License issued by Indian pharmaceutical Company Cipla to the countries namely Malaysia, Indonesia, Mozambique, and Zambia in year 2004 for the import of anti retroviral medicines for a period of two years. Indonesia has allowed using compulsory license for anti retroviral medicines named lamivudine and nevirapine. Mozambique country issued its generic version of medicine for HIV/AIDS drugs. In year 2005 Ghana and Eritrea country issued its generic version of medicine for anti retroviral medicines HIV/AIDS drugs respectively. In Year 2006 and 2007 Thailand, Rwanda and Brazil issued its generic version of medicine for curing heart disease by use of drug Plavix and Brazil country allowed for the import of generic drug Efavirenz from India. Also Rwanda country allowed for compulsory license in the form of Nevirapine, Zidovudine and Lamivudine named Triavir to treat HIV and AIDS which they were unable to manufacture locally. Natco Pharmaceutical a domestic generic medicine producer received first compulsory license in year 2012 for manufacturing Bayer Pharmaceutical's invented drug name Nexaver. (Chander et al., 2013)

XIV. Some Measure are Proposed to Strengthen the Compulsory License Regime in India as given below

1. Corporate social responsibilities:-Indian government shall have good joint efforts with most big pharmaceutical companies as an involvement in government funded healthcare mission in the form of corporate social responsibilities which would encourage them as an equal partner and by this way they can reduce the chances of patent abusing.
2. United State Act on intellectual property for protection of patent through government funding named Bayh-Dole shall be enforced in India, which may allow the Indian Government to grant compulsory licenses on inventions in some cases.
3. Indian Government shall exercise pressure on the innovation to the patent holder which may cut the price of the innovative product or may purchase innovated medicines from the producers of patent by drug price control mechanism or by negotiations.
4. Indian Patent Office must issue guidelines related to issue and interpretations of compulsory license which would result into reduction in ambiguity on provisions of compulsory license.
5. Low royalty & royalty free method: Compulsory license for manufacturing of generic version of patented drug are issued in crisis, emergency or on urgent basis when the drug is required on large scale and on economic price so medicine should be within the reach general public. Royalty in case of crisis, emergency or on urgent basis shall not be high as the burden of this would come on general public in increased price for. Marketing geographical location, quantity of product, time period of license, market value of product, and percentage of customers are the factors which shall decide the percentage of royalty. Countries of high & middle income group shall be paid high royalty for compulsory license because of low disease rate and vice versa. Compulsory license given on royalty free basis will result into decline of efficacy and production skills on patent inventions for further development of research & development. Society will be benefited when same medicines are

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available into the market, its prices would be less because of perfect competition into that area. Royalty for efforts to holder of patent must paid in reasonable amount with proper negotiations skills and by proper agreement. In case of critical illness drugs like cancer, AIDS, tuberculosis government shall purchase the patent from the holder of patent. Tax benefits and some incentives shall be given to holder of patent so that they can lower the price of innovated medicine. Government in underdeveloped countries can encourage patent holder for donation of patented medicines willingly. (Yang, 2012)

6. Research and development in pharmaceutical patents provides patent holder a kind of monopoly rights. If patent holder is not compensated adequately for cost on research and development activity incurred on development of a new product leads to decline in research and development activity. Patent holder is compensated in the form of royalty for innovations on patent by Government for use of innovation in case of compulsory licence without permission from holder of patent. "It is necessary to strengthen the system of compulsory licenses in the developing and least developed countries because of their inability/ inefficiency to cater to the needs of its people. And while the granting compulsory licensing over the patent protected drugs shall give monetary benefits to the patented pharmaceutical companies". As India is a developing nation and also by considering the various important judgments pronounced by the Honourable Supreme Court of India relating to manufacturing of drugs at an economic rates, The Indian Government should promote process patent rather than providing product patent as it creates monopoly condition in the market which leads to higher price of drugs. Providing product patent is violation of various rights like public health and access to medicines, which ultimately violates the human rights of the individuals.

XV. Conclusion

Developed countries Government limiting most developing countries not to issue compulsory licenses and expert from large pharmaceuticals feels that this policy would affect the research and innovation as patent holder would be unable to recover their amount invested in R&D activity. Opposite of this, NGO's has appreciated this policy of compulsory licensing on the perspective of good patient's health at an economic cost. In order to protect R&D and innovation, patent holder shall be compensated for developing the economic status of country, so this will help the innovator pharmaceutical company to shield their patents and accessibility for the developing countries. (Chander et al., 2013).The purpose of compulsory license lies in access to affordable drugs. Policies like drug price ceiling limit and control on profit margin on big pharmaceutical firm may control the patent abuse. With such policies general public shall access the medicines on an economic price. Countries foreign direct investment may get declined when country issue limits on the grant of compulsory license. Therefore government should put limit on compulsory license only in extreme cases in any country. Doha Declaration and Trade-Related Aspects of Intellectual Property Rights provisions give health benefits to the public on non discrimination basis. (Kaur & Chaturvedi 2015).The growing concern over compulsory license ultimately lies in country's urge to provide access to medicines at an economic cost. It is not disputed that voluntary licensing is potentially a powerful tool that developing countries including India can use to bypass patent laws and can provide their residents access to drugs mainly in some dangerous disease like cancer. Compulsory licensing breaks up monopolies and cartels agreements and sometimes provide their residents for access to life-saving drugs at affordable prices. Though India is not at a stage to analyze the impact of first compulsory license, experiences of countries which granted such licenses shows that compulsory license has the potentiality to effectively reduce the price of the drugs and increase the accessibility of medicines. (Bale, 2005).There have been a handful of decisions that have the potential to foster the unique lines of Indian jurisprudence that projects access to essential medicines as a fundamental public health consideration. A unique provision that exists in Indian Patent Laws which prohibits patent for the use of known substance throws light in the decision of Novartis Company Ltd. v. Union of India. (Cutler and Civil Appeal No. 2706-2716, 2013)

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Phenolic Compounds from Plants - An Important Class of Phytomedicine in Wrestle against Cancer- A Review

By Aloisio Mateus Fiuza Sanha, Satyender Kumar & Parmod Kumar Sharma

Galgotias University

Abstract- Phenolic and Polyphenolic are important compounds from the class of phytomedicine and are widely distributed in the plant kingdom. Over the years, an increasing amount of interest has been vastly drawn into the plant polyphenolic mainly because these compounds have shown tremendous efficacy in the treatment of oxidative stress-related diseases such as cancer. Currently, much medical investigations are conducted on plant phenolic for improving their identification and development for better therapeutic efficacy in the fight against different types of cancers. We aim to update and provide an extensive overview of the mechanism of action and the role of phenolic compounds in the treatment of tumor. The various databases used to conduct the literature survey are (Pub Med Central, Scopus, Research Gate, EMBASE, Google Scholar, Science Direct, Sci ELO, PLoS (Public Library of Science). In the first stage it includes different types of cancers and their biomarkers. In second stage, different phenolic compounds in plants and their role in the cancer treatment. Finally, to find out the mechanism of action and clinical status of phenolic compounds against different biomarkers and the mechanism of action of phenolic and polyphenolic compounds against cancer and its biomarkers with their antioxidant activity.

Keywords: *plant phenolic; antioxidant; anticancer; pro-oxidant.*

GJMR-B Classification: *NLMC Code: QV 766*



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Aloisio Mateus Fiuza Sanha [α], Satyender Kumar [σ] & Parmod Kumar Sharma [ρ]

Abstract- Phenolic and Polyphenolic are important compounds from the class of phytomedicine and are widely distributed in the plant kingdom. Over the years, an increasing amount of interest has been vastly drawn into the plant polyphenolic mainly because these compounds have shown tremendous efficacy in the treatment of oxidative stress-related diseases such as cancer. Currently, much medical investigations are conducted on plant phenolic for improving their identification and development for better therapeutic efficacy in the fight against different types of cancers. We aim to update and provide an extensive overview of the mechanism of action and the role of phenolic compounds in the treatment of tumor. The various databases used to conduct the literature survey are (Pub Med Central, Scopus, Research Gate, EMBASE, Google Scholar, Science Direct, Sci ELO, PLoS (Public Library of Science). In the first stage it includes different types of cancers and their biomarkers. In second stage, different phenolic compounds in plants and their role in the cancer treatment. Finally, to find out the mechanism of action and clinical status of phenolic compounds against different biomarkers and the mechanism of action of phenolic and polyphenolic compounds against cancer and its biomarkers with their antioxidant activity.

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I. Introduction

The term cancer is related to uncontrolled growth of abnormal cells in which the immune system fails to control these cells that leads to uncontrollable multiplication and spreadability to different parts of the body.[1] Despite the advancements in the diagnosis and treatment of cancer, [2] the mortality rate by cancer has been progressively increasing worldwide. [3] In 2018, the mortality by different cancers such as; Lung (1.76 million), Colorectal (8,62,000 deaths), Stomach (7,83,000), Liver (782,000 deaths), Breast (627,000 deaths). The number of deaths (9.6 million), new cases of cancers (17 million) in which male population (8.8 million) and female population (8.2 million) reported in 2018. It is expected that new cases will increase up to 27.5 million by 2040 representing 61.7% increment from 2018. [5] [6]

Author α σ ρ: Department of Pharmaceutical Sciences, School of Medical and Allied Sciences, Galgotias University, Greater Noida, Uttar Pradesh, 201308, India.
e-mails: satyender.kumar@galgotiasuniversity.edu.in, mateusfsanha93@gmail.com

II. Cancer and Types of Cancer

Melanoma skin cancer develops from the melanocytes usually on the chest and back part of the body. Basal cell and squamous cell cancers are the most predominant skin cancers and not spread to other parts of the body. [6] [7]

The oral cavity cancer develops in the mouth, while *oropharyngeal cancer* begins in the oropharynx. They develop from squamous cell carcinomas, verrucous, minor salivary gland carcinoma, and lymphoma. [7]

Lung cancer develops in lung tissues, especially in the air passages of cells lining and further categorized into non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), Mesothelioma. [8] [9]

Gastric cancer is triggered by Helicobacter Pylori, dietary patterns, socioeconomic status, genetic predisposition, environmental factors. [10] Colon and Rectal cancer are known as single tumor entity; hence, it is called colorectal cancer. Colorectal cancer involves the cancer formation in the colon, rectum and in the appendix. [11] [12]

Kidney cancer is abnormal kidney cell growth and further categorized into renal cell carcinoma, transitional cell carcinoma, nephroblastoma. [13]

Prostate cancer is the uncontrollable growth of the cells in the prostate gland. The inference of this cancer in men is higher as compare to women. The figures have shown that one (1) out of every eight (8) suffer from prostate cancer their life-time, and mainly men above 65 years of age). [13]

Urinary Bladder Cancer is the uncontrolled growth of the cells of bladder and without treatment cancer cells can spread to other tissues of the body. Bladder cancer includes urothelial carcinoma (transitional cell carcinoma), squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. [13] [14]

Leukemia is part of the heterogeneous group of cancers linked with the hematopoietic system and characterized by uncontrolled proliferation of leukocytes in bone marrow. It is divided into lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML). [15] [16]

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Ovarian cancer is not necessarily from ovarian but can originate from the fallopian tube. There are various types of ovarian cancers such as epithelial ovarian tumors, ovarian germ cell tumors, and ovarian stromal tumors. [17] [18]

III. Different Cancer Biomarkers

Biomarkers are biological molecules present in blood, tissues, lymph and they serve as a signaling agent for normal or abnormal functioning of the body. Biomarkers include proteins, nucleic acid, antibodies, peptides and others that give the indication of disease due to alteration in the germline or somatic mutations, transcriptional and post-translational alteration and also changes like in gene expression, metabolic and proteomic changes can also serve as biomarkers. [19]

Biomarkers can be classified based on disease state (prediction biomarkers, detection biomarkers, diagnostic biomarkers, prognosis biomarkers), based on biomolecules (DNA biomarkers, RNA biomarkers, protein biomarkers, and based on other criteria (imaging biomarkers, pathological biomarkers, *in-silico* biomarkers). [20]

Cancer biomarkers can further be categorized into the following classes:

a) Prognostic biomarkers

Prognostic biomarkers which help in predicting the cancer and its nature course that differentiate between good and poor tumor outcome as well as how strong the treatment is to be done, [21] *Predictive markers* provide upfront information about the possible success or failure of a specific treatment, [22] *Pharmacodynamic markers* provide information on the effectiveness of the drugs on the body which incorporate the drug effect on the target cancer cell and also provide the effect of the body towards the drug including the absorption, distribution, metabolism and elimination of the drug. These markers are also important in the dose optimization which does not reach to the cytotoxic levels, diagnosis *biomarkers* are very important due to the fact that they are probably present in the early stages of cancer which include calcitonin in medullary thyroid cancer. [20]

b) Ovarian cancer biomarkers

Various biomarkers are currently being used in the efficient detection of ovarian cancer as shown in (Fig. 1), and new generation of biomarkers for ovarian cancer is under clinical trial. [23] [24]

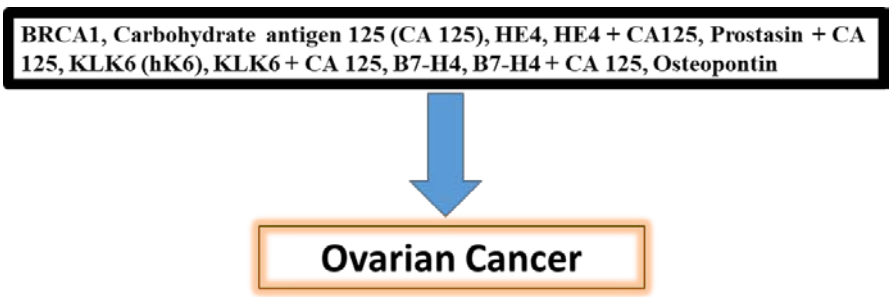


Fig. 1: Schematic representation of different biomarkers used in the detection of ovarian cancer. Breast cancer type 1 susceptibility protein (BRCA1), Carbohydrate antigen 125 (CA 125), Human epididymis protein 4 (HE4), HE4 + CA125, Prostasin + CA 125, Kallikrein-related Peptidase 6 (KLK6) (hK6), KLK6 + CA 125, B7-H4, B7-H4 + CA 125, Osteopontin biomarker which help in prediction of ovarian cancer.

c) Acute myeloid leukemia biomarker

Various biomarkers are currently being used in the efficient detection of ovarian cancer as shown in (Fig. 2). [25] [26]

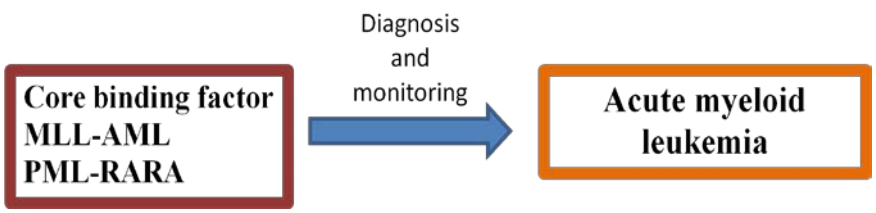


Fig. 2: Schematic representation of different biomarkers used in the detection of acute myeloid leukemia. MLL-AML, Promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) markers for diagnosis and monitoring of acute myeloid leukemia.

d) Biomarkers in urinary bladder cancer

For the detection of bladder cancer, various biomarkers have been used as shown in Fig. 3). [27] [28]

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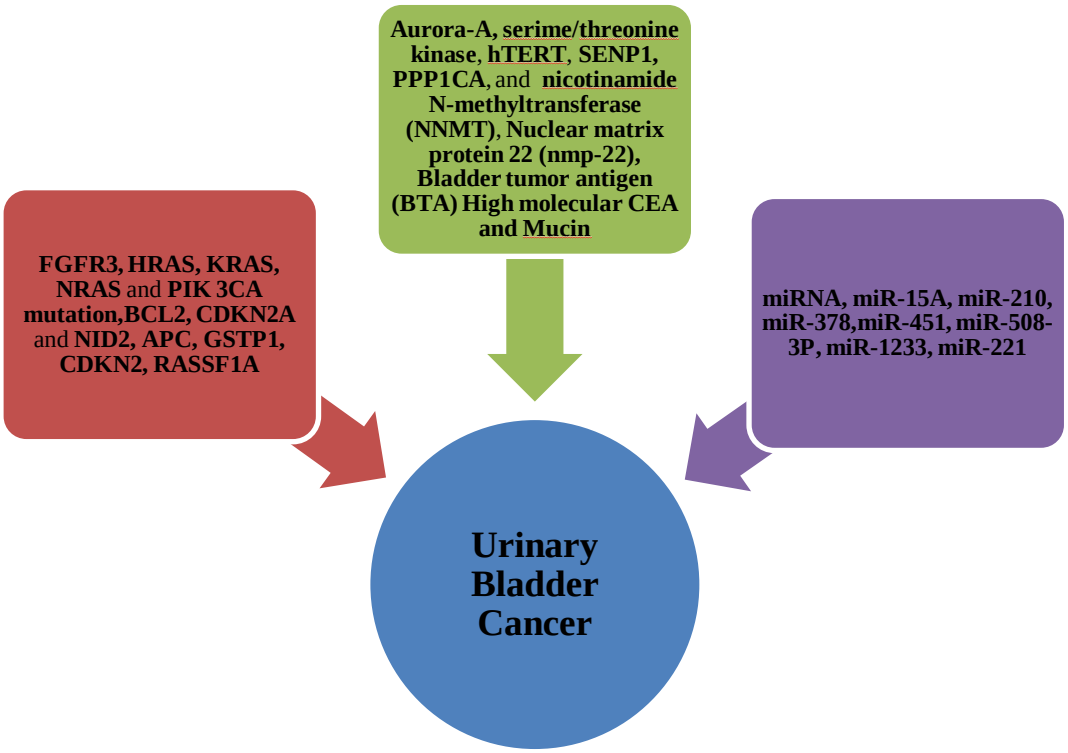


Fig. 3: Schematic representation of different biomarkers used in the detection of bladder cancer. Fibroblast growth factor receptor 3 (FGFR3), gene v-Ki-ras2 Kirsten rat sarcoma (KRAS), HRAS, , NRAS and Phosphatidylinositol 3-kinase (PIK 3CA mutation),B-cell lymphoma 2 (Bcl2), cyclin-dependent kinase Inhibitor 2A (CDKN2A) and Nidogen-2 (NID2), Adenomatous Polyposis Coli(APC), Glutathione S-Transferase P1(GSTP1), cyclin-dependent kinase Inhibitor 2A (CDKN2A), RAS association domain family protein 1A (RASSF1A) and tissue inhibitor of metalloproteinases-3 (TIMP3). RNA markers includes: Aurora-A, serine/threonine kinase, Telomerase reverse transcriptase (Htert), Sentrin-specific protease 1 (SENP1), protein phosphatase 1 catalytic subunit alpha (PPP1CA), and, nicotinamide N-methyltransferase (NNMT), Nuclear matrix protein 22, Bladder tumor antigen (BTA) High molecular CEA and Mucin. Biomarkers in Renal Cell Carcinoma include: miRNA, miR-15A, miR-210, miR-378, miR-451, miR-508-3P, miR-1233, miR-221.

e) Biomarkers in colorectal cancer

The following markers (Fig. 4) are used in the detection of colorectal cancer. [29] [30] [31] [32]

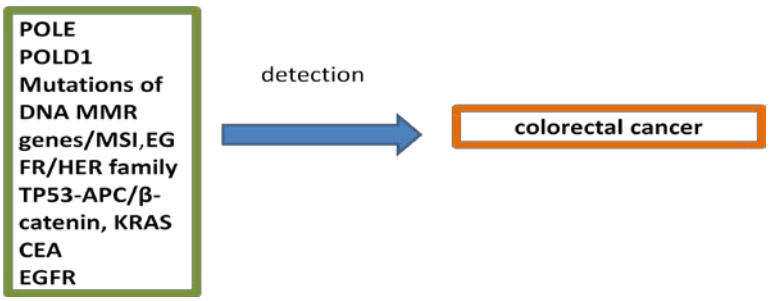


Fig. 4: Schematic representation of different biomarkers used in the detection of colorectal cancer. POLE (DNA polymerase epsilon) and POLD1 (DNA polymerase delta 1) mutations, DNA MMR genes/MSI, EGFR/HER family, TP53-APC/β-catenin, KRAS (Kristen rat sarcoma virus), Carcinoembryonic Antigen (CEA), Epidermal growth factor receptor (EGFR).

f) Biomarkers for detection of lung cancer

For the detection of lung cancer, various biomarkers are used as shown in Fig. 5 [30] [9] [33] [34]

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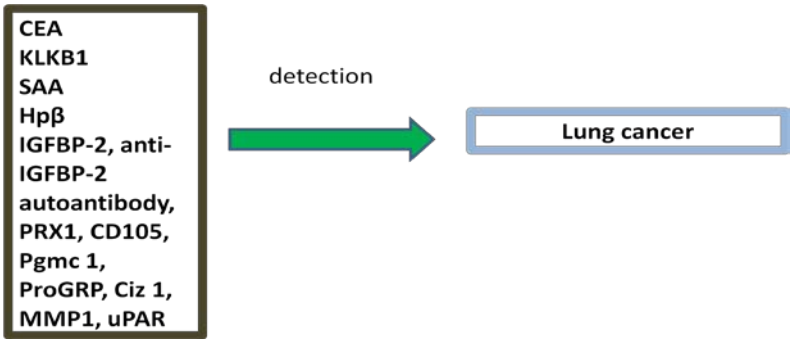


Fig. 5: Schematic representation of different biomarkers used in the detection of lung cancer. CEA (Carcino Embryonic Antigen), Plasma Kallikrein (KLKB1), Serum Amyloid A (SAA), Haptoglobin β Chain (Hpβ),insulin-like growth factor binding protein 2 (IGFBP-2), anti-IGFBP-2 autoantibody, peroxiredoxins (PRX1), CD105, Pgmc 1, Pro-gastrin-releasing peptide (ProGRP), Ciz 1, MMP1, Urokinase plasminogen activator receptor (UPAR).

g) Biomarkers in pancreatic cancer

The following (Fig. 6) represent genetic biomarkers used in pancreatic cancer detection along with (tissues biomarkers). [35]

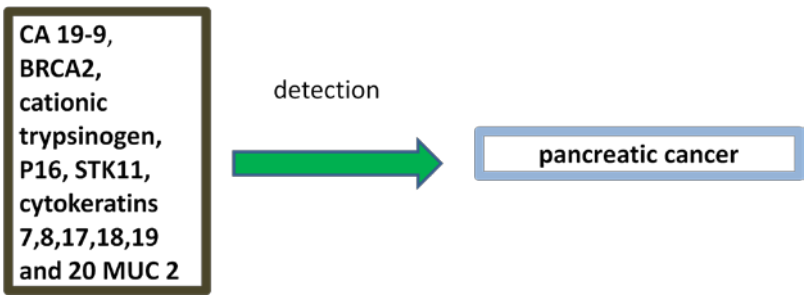


Fig. 6: Schematic representation of different biomarkers used in the detection of pancreatic cancer. Carbohydrate antigen 19-9 (CA 19-9), BRCA2, cationic trypsinogen, P16 (tumour suppressor protein), serine/threonine kinase 11 (STK11), cytokeratins 7, 8, 17, 18, 19 and 20 MUC 2.

h) Biomarkers in cervical cancer

The following biomarkers are used for detection of cervical cancer (Fig. 7). [24]

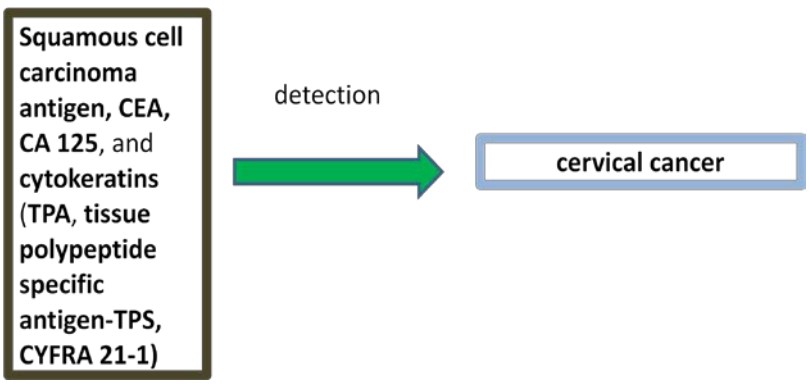


Fig. 7: Schematic representation of different biomarkers used in the detection of cervical cancer. Squamous cell carcinoma antigen, CEA, CA 125, and cytokeratins (TPA, tissue polypeptide specific antigen-TPS, CYFRA 21-1).

i) Biomarkers in breast cancer

For the detection of breast cancer the following biomarkers are used (Fig. 8). [36]

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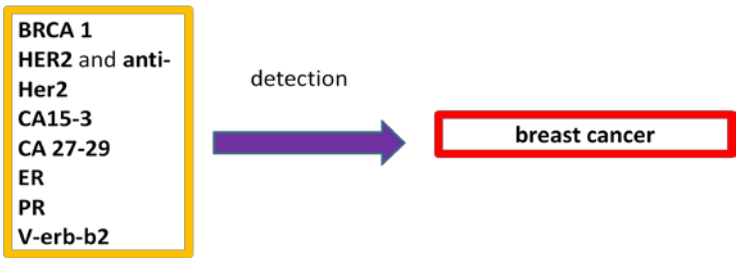


Fig. 8: Schematic representation of different biomarkers used in the detection of breast cancer. BRCA 1, HER2 and anti-Her2, Carbohydrate antigen 15-3 (CA15-3), Carbohydrate antigen 27-29 (CA 27-29), Estrogen receptor (ER), Progesterone receptor (PR).

IV. Phenolic Compounds in the Prevention of Cancer Formation

The factors that can contribute significantly to the formation of cancer include *intrinsic risk* (random error in DNA replication), *extrinsic risk* further divided into *endogenous risk factors* (biological aging, genetic susceptibility, DNA repair mechanism, hormones, growth factors, inflammation) and *exogenous risk factors* (radiation, chemical carcinogens, tumor-causing viruses, bad lifestyle like smoking, lack of exercise, nutrient). [37] [38]

Phenolic compounds are well documented for their anticancer properties by reducing intrinsic and extrinsic factors and by interfering with the metabolism of pro-carcinogens by regulating the expression of cytochrome P450 enzymes. Increase the excretion by increasing the expression of conjugating enzymes phase II. Production of toxic quinones which is the substrate of this enzyme in the body, thus, their absorption can stimulate detoxication activity which will result in protection against toxic xenobiotics. Polyphenolic compounds like quercetin, catechins, isoflavones, lignans, Flavanones, red wine polyphenols, resveratrol, and curcumin can stimulate apoptosis of tumor cells and inhibit angiogenesis; thus reducing the growth of tumor. [39]

The increasing threat from the free radicals in current days enhances the importance and use of phenolic compounds. Free radicals can worsen the already existing pathological condition, trigger the onset of action of disease and eventually develop new pathological conditions. Thus, phenolic compounds can play an important role in preventing this disease e.g. cancer, neurodegenerative diseases. Phenolic compounds offer a prominent capacity in providing the oxidative balance in the body by protecting against oxidative reactions, oxidants, and reactive species. Phenolic compounds are chemically different. Thus, they show their action through different polyvalence reactions, by enhancing the potential of some compounds, blocking the side effects of other compounds and presenting other biological activities used as antibacterial, anticancer, anti-inflammatory, diabetes, hypertension, obesity, Alzheimer. [40] Many components from plants are subjected to an exhaustive study on their antioxidant properties. [41] The importance of plants is vastly used in the treatment and prevention of cancer. [42] Antioxidants act by complexing metal ions, scavenging of free radicals, and the decomposition of peroxides. Most of the anticancer drugs available today about 60% derived from the plant source. [43] [44]

Phenolic is made up of aromatic ring which is made up of one or more hydroxyl group, and it is present in many flowering plants, vegetative organs, in flowers and many fruits, cereals, seeds. [45] The phenolic hydroxyl group, however, is influenced by the presence of the aromatic ring. Due to this aromatic ring, the hydrogen of the phenolic hydroxyl is labile, which makes phenols weak acids. [46] These compounds action is not solely owned by their antioxidant effects but also antiviral, immune-stimulant, antibacterial, estrogenic effects, cytotoxic properties in various tumor cells. [47]

Plant phenols are grouped into simple and complex phenolic acids. Simple phenolic acids are divided into benzoic acid and cinnamic acid. The complex phenolic acid is divided into three classes (Tannins, Flavonoids, and Stilbenes). [48] Phenolic compounds have been classified into different groups as described below in Fig. 9.

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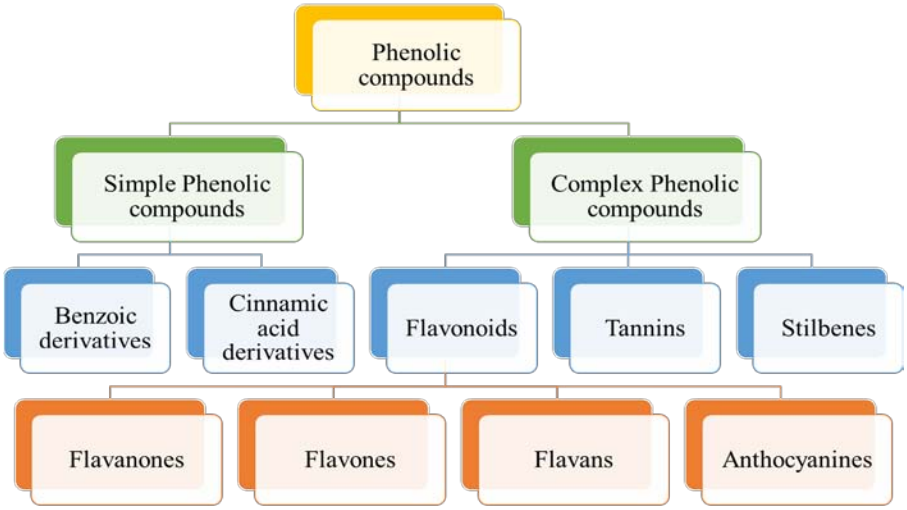


Fig. 9: Classification of the phenolic compounds.

V. Mechanism of Action of Various Phenolic Compounds in Cancer Development

Phenolic compounds have shown cancer prevention ability in the different type of cancers.

a) Activity of phenolic compounds against prostate cancer

Delphinidin has the ability to inhibit cell growth and promote caspase-mediated apoptosis which leads to tumor size reduction, this was observed by *in-vitro* human cell lines and *in-vivo* murine models assay, 7-hydroxymatairesinol which can inhibit tumor growth and stop tumor cell proliferation this was observed by *in-vivo* murine assay, Caffeic acid through LNCap cell lines assay have shown the ability to inhibit tumor cells growth, Ferulic acid by PC-3 cell lines assay have presented inhibitory effect on tumor size ultimately leading to apoptosis. [49]

b) Activity of phenolic compounds against leukemia cancer

Delphinidin-3-sambubioside can lead to inhibition of Caspase-3,-8 and 9 ultimately leading to apoptosis activation which was observed by *in-vitro* human cell lines assay, Podophyllotoxin and polyethylene by *in- vitro* human cell lines have shown better tumor inhibition as compared to podophyllotoxin alone, [50] Podophyllotoxin and fatty acids analogs possess cytotoxic effects towards cancer cells and low toxicity towards sane cells, this was seen by *in-vitro* human cell lines assay. [51]

c) Activities of phenolic compounds against lung cancer

Cyaniding-3- rutinoside and cyaniding-3-glucoside by *in-vitro* human cell lines assay have shown dose-dependent tumor inhibitory effect, p-coumaric acid by A549 assay have present tumor inhibitory activity, Quercetin in PEG 400 liposomes possess Tumor inhibition activity which leads to apoptosis has seen in *in-vivo* murine models assay. [52]

d) Activity of phenolic compounds against gastric cancer

Cyanidin-3-0-glucoside through *in- vivo* human cell lines assay demonstrated a decrease in cell proliferation and morphological changes which ultimately lead to apoptosis. [53]

e) Activity of phenolic compounds against skin cancer

Ferulic acid through *in-vivo* murine cells assay have shown the ability to prevent the tumor formation, Kraft lignins by in-vitro human cell lines and in-vivo murine cell lines assay have shown Adsorption to nitrosamines DNA protective effect against tumor, Resveratrol have shown inhibition of pre-neoplastic lesions and tumorigenesis inhibition has seen in *in-vivo* murine xenografts assay. [54]

f) Activity of phenolic compounds against colon cancer

Cinnamic acid through HT-29 cell line assay have shown inhibition of tumor growth, p-coumaric acid through SW-620 cell line assay has shown inhibition of tumor size growth. [55]

g) Activity of phenolic compounds against breast cancer

Gallic acid can lead to tumor size reduction has seen in MDA-MB-231 cell line assay, Caffeic acid can cause inhibition of tumor growth, and apoptosis demonstrated by MDA-HB-231 assay. [56]

h) Activity of phenolic compounds against bladder cancer

Dicoumarol can lead to enhancement of the anticancer effect of the drug which is shown by *in-vitro* human cell line assay. [57]

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i) Activity of phenolic compounds against renal cell cancer

Daphnetin with the help of *in-vitro* human cell line assay has shown activation of $_{P}38$ cell cycle arrest, coumarin through epidemiological studies assay has shown enhancement of the anticancer effect of various drugs used in renal carcinoma. [58]

Due to the difference in the structures and molecular targets the anticancer activity differs among the various phenolic compounds. Antioxidant and in-vitro anticancer activities of phenolics isolated from sugar beet molasses. Phenolic compounds that possess a greater number of hydroxylic groups show better anticancer activity in comparison with $–OCH_3$ moieties. [59] Plant polyphenols has shown therapeutic effects as antioxidants and free radicals scavengers not only against cancer but also against pro-oxidation, anti-diabetic, LDL oxidation, antibacterial, antiviral, anti-inflammatory, anti-allergic, lipid-lowering, and anti-aging. [60] Cancer development is divided into various stages for example initiation, promotion, progression, invasion, and metastasis. The mechanism of action of phenolic compounds in various stages of cancer progression is described in Fig. 10. [61]

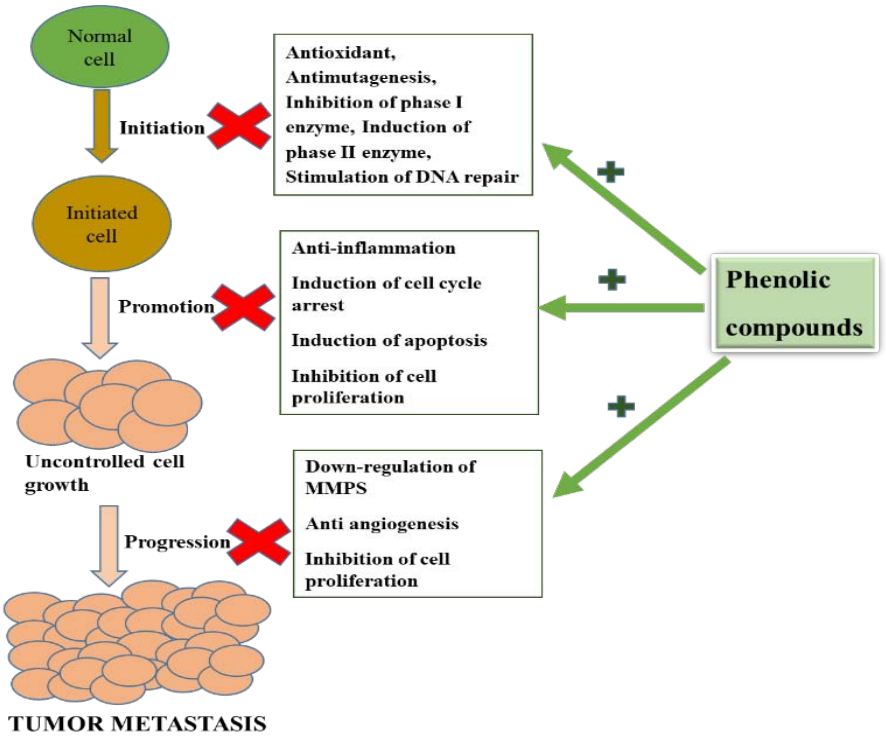


Fig. 10: Mechanism of action of phenolic compounds in tumor development.

Phenolic compounds plays different role against oxidation pathways and free radicals, oncogenic pathway, tumor suppression pathway, cytokine cell differentiation pathway, matrix metalloproteinases, Cyclin-dependent Kinases (CDKs) and Anaphase-promoting enzymatic complex (APC/C), p53, Bcl-2 markers, estrogen receptors (ER's), HER2 markers, TPA and DMBA markers against cancer. [62]

VI. Phenolic Role against Oxidation Pathways and free Radicals

Oxidative stress means lack in the balance between oxidant by-products and the antioxidant defense system which is directly associated with metabolism and the antioxidant defense mechanism. [63] Enzymes like catalase, superoxide dismutase, and glutathione peroxidase constitute the antioxidant defense system. [64] In some disease condition or in depletion of antioxidant these controls the mechanism is not sufficient and oxidant by-products which can lead to DNA damage protein and lipids. [65] Mitochondria, phagocytic cells, peroxisome fatty acid, and certain enzymes are responsible for the production of oxidant by-products in cells. Exposure to cigarette smoke, excessive iron and copper intake by diet can as well lead to oxidative stress. Superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, chain reaction mechanism in lipids and nitric oxide radicals outstand as the most important oxidative by-product of cells. [65] [66]

The chain reaction mechanism can be classified into the following steps:

- Initiation step (where the free radicals are formed);
- Propagation step (where free radicals converted into other radicals);
- Termination step (where two radicals combine with the formation of stable products).

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Initiation:

$ROOH \leftrightarrow ROO\cdot + H$

$ROOH \leftrightarrow RO\cdot + OH^-$

$2ROOH \leftrightarrow RO\cdot + H2O + ROO\cdot$

Propagation

$R\cdot + O2 \leftrightarrow ROO\cdot$

$ROO\cdot + RH \leftrightarrow ROOH + R\cdot$

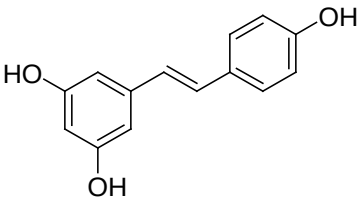
Termination

$ROO\cdot + ROO \leftrightarrow ROOR + O_2$

$RO\cdot + R \leftrightarrow ROR$

Phenolic compounds often referred to polyphenols are compounds with one or more aromatic ring(s) having hydroxyl substituent(s), and obtained from the plant secondary metabolite. The antioxidant activity varies depending on the structure of the compound. Flavonoids stand as the most prominent antioxidant compound as compared to others because they scavenge reactive oxygen species and nitrogen-reactive species in a much faster rate. They also scavenge superoxide, hydroxyl, peroxy radicals, peroxynitrous acid, and hypochlorous acid. Despite the tremendous advantages of phenolic compounds as an antioxidant agent, only a certain number of phenolic compounds have been approved for used in formulations and food products due to the risk of toxicity or carcinogenic effect. [67]

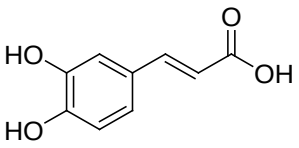
Degenerative diseases like arteriosclerosis and cancer are the result of free radicals and lipid peroxidation. A successful antioxidant activity of a phenolic compound against lipid oxidation is associated with the free radical scavenging activity of the phenolic compound. [68] The action of phenolic compounds in scavenging free radicals is due to their structure base on the fact that phenolic hydroxyl groups are prone to donate a hydrogen atom or an electron to a free radical. Also, because extended conjugated aromatic system to delocalize an unpaired electron. e.g., *Resveratrol,* a phenolic compound acts as an antioxidant found in grapes, red wine, peanuts, chocolate, certain berries, and possess a strong antioxidant effect, having large number of health benefits in various studies. [66]



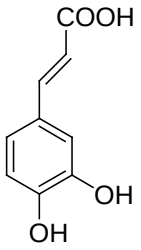
Resveratrol

a) *Phenolic role against the oncogenic pathway*

The oncogene is the result of mutations in the proto-oncogenes. This mutation allows oncogenes to make protein coding which allows cancer cells to proliferate and survive in the different environment. There is no need for the mutant B-Raf to translocate and associate with Ras protein to show enzymatic activity. [69] Thus, this results in uncontrolled proliferation of cancer cells which results in malignant metastatic tumor formation. [70] Various compounds have demonstrated their capacity in inhibiting cancer proliferation, for example *caffeic acid* inhibited metastasis of cancer in the colon. In the same way protocatechuic acid inhibited NF-Kβ and MAPK does control the proliferation of lung and gastric carcinoma cells. *Ferulic acid and caffeic acid* phenyl ester have shown down regulation of phosphorylated P13K and AKT which inhibited melanoma cells proliferation as well as induced apoptosis. [71]



Caffeic acid



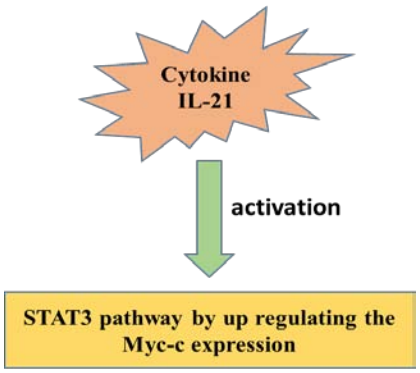
Ferulic acid

b) *Phenolic role against tumor suppression pathway*

The function of a tumor-suppression gene is to protect the normal cells or healthy cells by preventing oncogenic transformation into cancer or unhealthy cells. The example of tumor suppressors includes p53, PTEN, Rb proteins which prevent DNA damage caused by dyes, high-intensity radiation. [72] Despite this action, tumor suppressors also help in scavenging the damaged cells through the process of apoptosis. Resveratrol, a stilbene *compound* can also increase the expression of p53 in cervical cancer and inhibit the growth of ME180 cells. [73] [74]

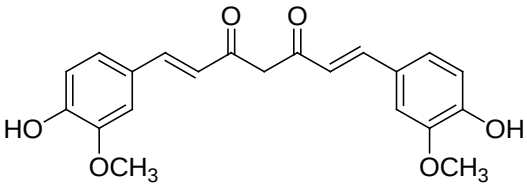
c) *Phenolic role against cytokine and cell differentiation pathways*

Interferons, interleukins, tumor necrosis factor, lymphokines are known as cytokines and are involved in cell signaling, development, and immune responses. The release of these cytokines in uncontrolled fashion will result in either oxidative stress or chronic inflammation, thus malignancy in the normal cells. [75]



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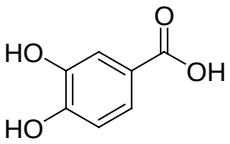
Myc-c is the gene that regulates 70% of cancers. The mutation of Myc-c will result in unsuccessful control of differentiation of cells. Myc-c is actively involved in cell cycle regulation metabolism, differentiation, and cell growth. Thus, the phenolic compounds for example curcumin that can inhibit cytokines proliferation are important anticancer agents. [75] [76]



Curcumin

d) Phenolic role against matrix metalloproteinases enzyme

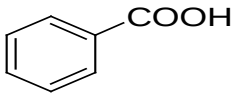
Cancerous cells exhibit high degradation of extracellular matrix of a healthy cell to promote tumor invasion and metastasis; this is the characteristic of matrix metalloproteinase which are endopeptidase. Molecules like *protocatechuic acid, ferulic acid* are capable of inhibit MMP and can also stop growth of tumor cells. [77] The derivatives of cinnamic acid for example CAA and CAPE can inhibit MMP-9 and MMP-2 activities, thus prevent hepatoma cells growth and metastasis. Hence, phenolic derivatives with MMP inhibition characteristics can prevent metastatic spreading of cancerous cells. [78]



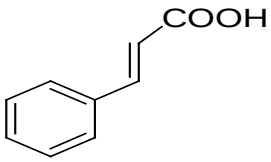
Protocatechuic acid

e) Phenolic role against Cyclin-dependent Kinases (CDKs) and Anaphase-promoting enzymatic complex (APC/C)

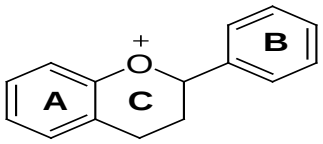
The regulation of CDK complexes is the result of binding of p21 and p27 with CDK, thus, the cell cycle activity is controlled due to the polyphenolic modulating activity on cyclins, APC/C or CDK. [79] In colon cancer polyphenolic compounds have shown cell-cycle arrest activity in S and G2/M phases and HCT-116 cells. The decrease in cyclin A and D1 levels by polyphenolic compounds for example red grape wine *polyphenol,* phenolic acids, flavonoids, carotenes causes cell-cycle arrest in MCF-7 cells in breast cancer. [80]



Hydroxybenzoic acid



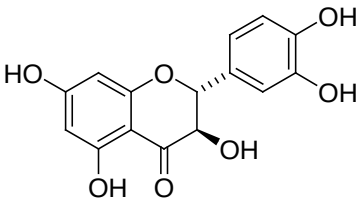
Hydroxycinnamic acid



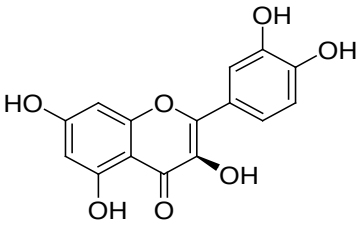
Flavonoids

f) Phenolic role against Tumor protein p53 (simply p53)

In various functions associated with cellular stress, cell proliferation, and death the tumor suppressor p53 is activated. Several researches have shown that plant phenolic and extracts possess the ability to activate p53 or p53 mediated pathway. In the first approach demonstrated that plant phenolic like *taxifolin* and *quercetin* possess the ability to disrupt interactions between Mdm2 and p53, thus, the degradation of p53 is completely prevented. [81]



Taxifolin

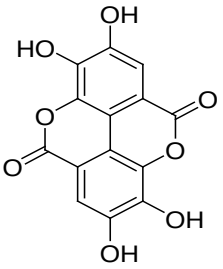


Quercetin

g) Phenolic role against (B-cell lymphoma) Bcl-2marker

The use of polyphenolic compounds for example Ellagic acid (EA) can decrease the expression of Bcl-2 in breast cancer and increase p21 levels by phosphatidylinositol-3, 4, 5-triphosphate-3-phosphatase which lead to tumor apoptosis. [80]

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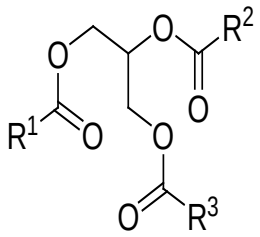
Ellagic acid

h) Phenolic role against Estrogen receptor (ER)

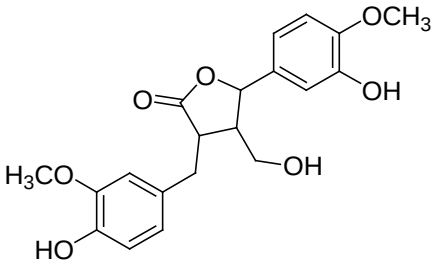
The effect of polyphenolic compound on estrogen is mainly due to the similar structure of flavonoids, isoflavones, Lignans and estrogen. Epigallocatechin gallate (EGCG) participates in the regulation of ER by down regulating the ER-α protein, gene promoter and mRNA actions in MCF-7 and ER. [80]

i) Polyphenolic role against Human epidermal growth factor receptor 2 (HER2)

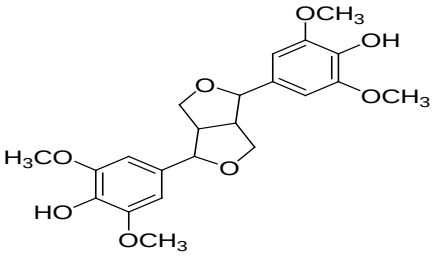
HER2 can spread by homo-or hetero-dimerize in addition with other HER upon its activation by activating P13K/AKT and Ras/MAPK. Polyphenolic compounds for example extra-virgin olive oil polyphenols, lignans can decrease HER2 activation or they can inhibit HER2 expression. The blocking of HER2 occurs by preventing ATP to bind with tyrosine kinase, suppression activity on pathways of HER2/HER3-PI3K/AKT, and another mechanism also includes the inhibition of binding between HER2-Hsp90.[80]



Olive oil



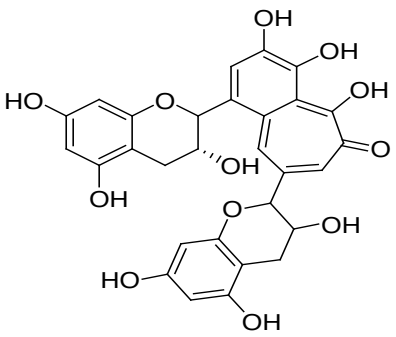
Lariciresinol (LAR)



Syringaresinol (SYR)

j) Polyphenolic compounds role against TPA and DMBA markers

The promoter of 12-O-tetradecanoyl phorbol-13-acetate (TPA) is inhibited by phenolic compounds which include protection against UVB light and induce apoptosis. Polyphenols for example *polyphenol* of green tea tannins, curcumin, phenolic acid, polyphenols in black tea and green tea can inhibit 7, 12-dimethyl benzene (a) anthracene (DMBA) even after the process was already initiated and TPA promotion has taken place. [81] Polyphenols can inhibit the cellular signaling in NF-kB, thus, results in apoptosis by the activation of DNA-PK-p53. [82] The inhibition DMBA/TPA-induced skin cancer can result in the inhibition of the skin tumor by blocking the inflammation promoter which includes interleukins which decreased Ha CaT cells by blocking the pathways of MAPK. The inhibition of 13 cis-retinoic acid also contributes in inhibition of skin tumor. [83] [84]



Theaflavin

Various anticancer activities of phenolic compounds against different pathways involved in cancer have been shown in the Fig. 11.

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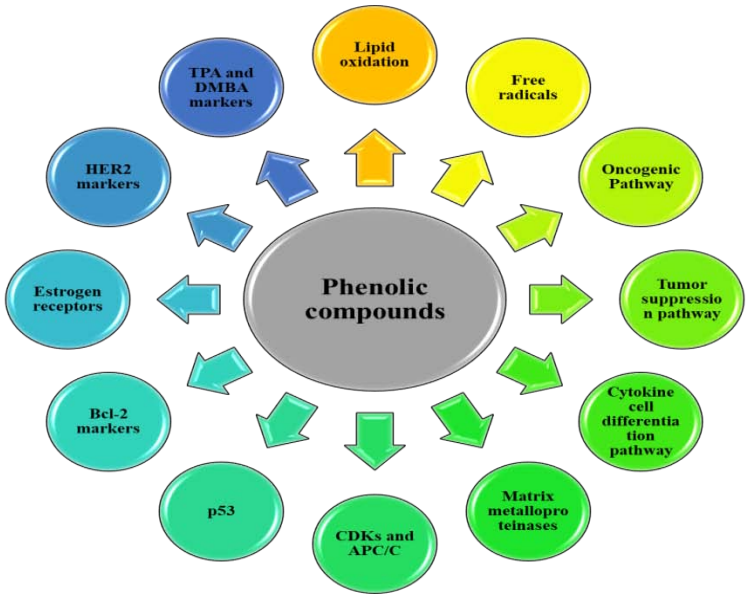
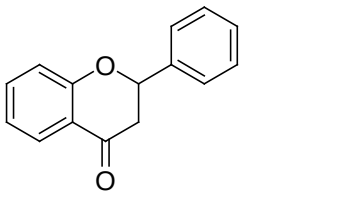


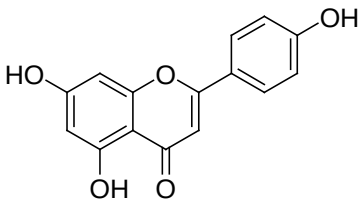
Fig. 11: Schematic representation of the role of phenolic compounds in Cancer.

VII. Flavonoids Role in Cancer

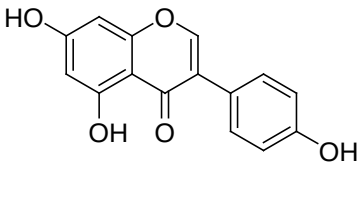
They are polyphenols with 15 carbon atoms, two aromatic rings bound through a three carbon chain (*C6-C3-C6*) which can eventually be part of a third ring. The chemical diversity of these compounds derived from this carbon skeleton. These compounds can exist in free or conjugated forms in nature esterified to one or two sugar molecules through one hydroxyl group (O-glucosides, O-Gluc). [85] They inhibit the formation of reactive species by chelating the metal ion, for example, iron and copper. Flavonoids can also present bio-molecular damage by peroxynitrite in vitro, inhibit activation of the carcinogenic metabolite, cell-cycle arrest through apoptosis, and prevent proliferation and angiogenesis. *Apigenin*, it stops the cell adhesion and invasion, decreases diolepoxide 2 formations, inhibits mitochondrial proton *F0F1-AT Pase/ ATP*, inhibits prostaglandin and IL-6, 8 production, prevents expression of intercellular adhesion *molecule-1 (ICAM-1). Genistein, luteolin, quercetin*, and *silymarin,* has shown antimutagenic and antiangiogenesis activities. Sylimarine can inhibit apoptosis and inhibit protein kinases whith *MAPK*. [86] Quercetin anticancer activity is the result of its action on caspases-3 inhibition, lymphocyte tyrosine kinase inhibition, telomerase inhibition, protein kinase inhibition and its effect on increasing the expression of quinine oxide reductase, nicotinamide adenine dinucleotide phosphate. *Daidzein, hesperetin, Kaempferol, and myrcetin* have presented anti-inflammatory characteristics. [87]



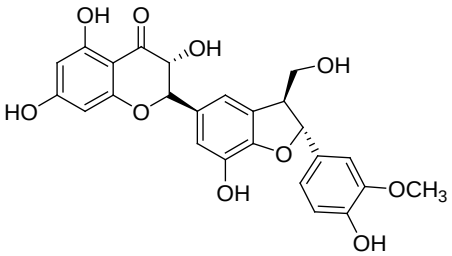
Flavonol



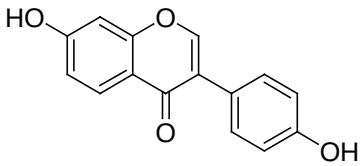
Apigenin



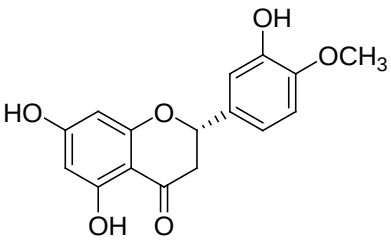
Genistein



Silymarin

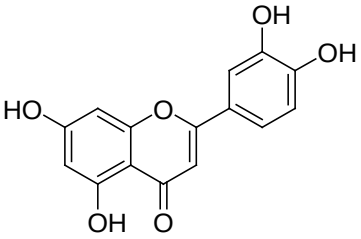


Daidzein

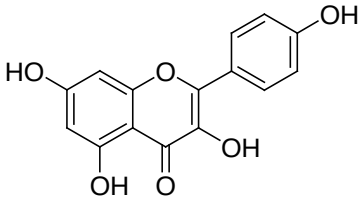


Hesperetin

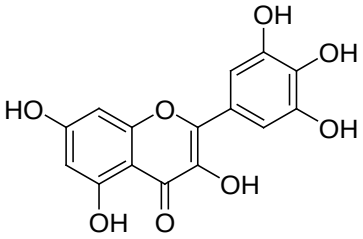
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Luteolin



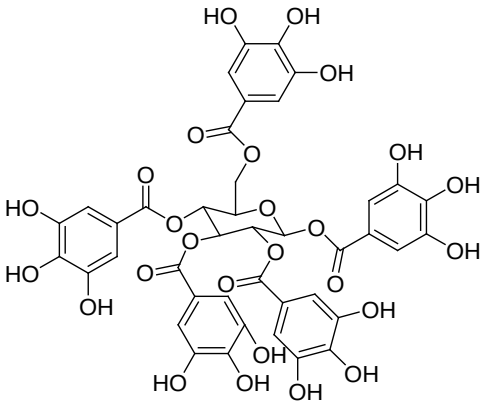
Kaempferol



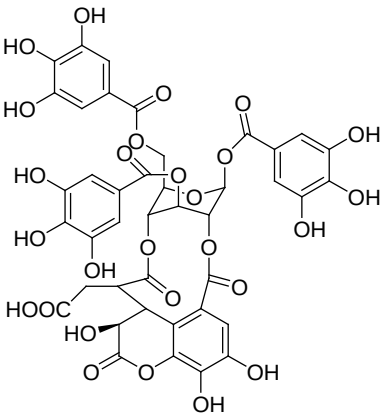
Myricetin

a) Tannins activity in cancer

Due to the presence of many hydroxyl groups such as orthodi-hydroxyl, tannins have shown a strong antioxidant activity against cancer. *Gallatin* is very efficient when tested against cancer in various animal models. The four *(4) ellagitannins*, 2 chromone gallates inhibit phosphorylation of extracellular signal protein kinase and P38 kinase by decreasing AP-1 and phosphoinositide 3-kinase (P13K), thus, stop epidermal growth factor which includes cell transformation. *Chebulinic acid* regulates transcriptional activation of an erythroid gene, for example, *gamma-globin*, *NF-E2 gene*, thus, inhibits differentiation in leukemia *K562* cells. *Casuarinin* inhibit progression of the cell cycle in *G0/G1* which results in apoptosis in breast cancer. [74]



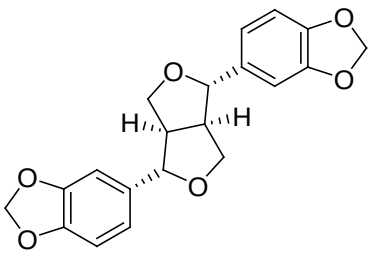
Gallotanin



Chebulinic acid

b) Stilbenes activity on cancer

They possess two aromatic rings linked by an ethene bridge. Resveratrol participates in all phases of carcinogenesis which include initiation, promotion, and progression of the tumor. Resveratrol can inhibit tumor cell growth by *inhibiting protein kinase activation*, *β-catenin expression down-regulation*, *caspases activation*, *NF-kB* and *AP1* blockage. Resveratrol can as well inhibit expression in *LNCaP* in prostate cancer cells. [88]



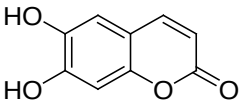
Sesamin

c) Lignans activity on cancer

These are dimmers having two C_6-C_3 units from the tail-to-tail linkage of two conifers. Example of this compound includes Sesamol and its glucoside. [89] Lignans have presented antimutagenic activity regulation of enzyme expression, antiangiogenic activity which can result in cell-cycle arrest and apoptosis in breast cancer. *Sesamin* has shown an effect on leukemia, breast and stomach cancer by acting as an antioxidant, triggering apoptosis and cell-cycle arrest. [90]

d) Coumarins activity on cancer

Coumarins along with *7-hydroxycoumarin* can inhibit cell proliferation and stop cell-cycle; thus, result in apoptosis. *Esculetin* (6, 7-hydroxycoumarin) can inhibit lipoxygenase and prevent the proliferation. [91]

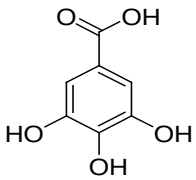


Esculetin

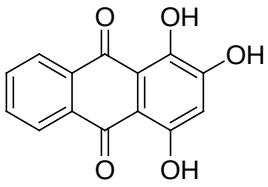
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e) Phenolic acids activity on cancer

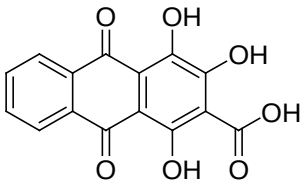
It counts for about 30% of dietary polyphenols and second most abundant in the polyphenolic family. Phenolic compounds have been divided into various classes, for example, Hydroxycinnamic acid including caffeic acid, ferulic acid and also into Hydroxybenzoic acid, for instance, *gallic acid*. [92] All these compounds have shown efficacy as an anticancer and anti-metastatic agent as well as effects on mesenchymal characteristics of cancerous cells. [93] [94] [95] Various phenolic drugs are obtained from the botanical source and few of these drugs.



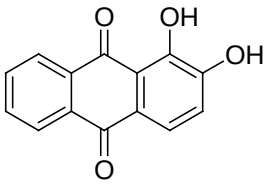
Gallic acid



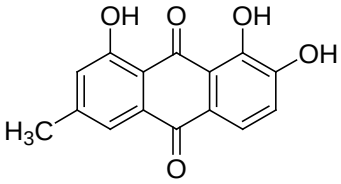
Purpurin



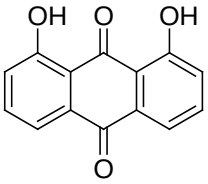
Pseudopurpurin



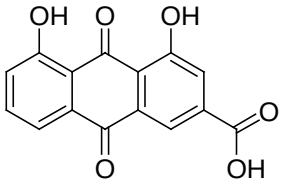
Alizarin



Emodin



Chrysazine



Rhein

f) Quinones activity on cancer

These are phenolic antioxidants obtained naturally. *Purpurin*, and *alizarin* were the most effective quinones. *Emodin, chrysazine, rhein, chrysophanol*, and *aloe-emodin* were also active but with less great extent due to the absence of ortho-dihydroxy structure. While catechol structure in various phenolic compounds and ortho-dihydroxy structure in hydroxyanthraquinone enhances the scavenging properties of phenolic molecules, on the other hand, glycosylation decreases the scavenging effects of hydroxyanthraquinone. [96] *Emodin* can inhibit cell-cycle and cause apoptosis by inhibiting casein kinase 2 and urease, inhibit DNA binding, thus blocking the signal transduction pathways. [97]

Phenolic compounds from natural sources enrolled under different phases of clinical trials for the detection and treatment of various types of cancers discussed in Table 1.

Table 1: Phenolic compounds under clinical trial for detection and treatment of various types of cancers.

Phenolic Compound	Type of Cancer	Phase	Clinical Trial id	Status
Caffeic acid	Esophagus cancer	III	NCT 03070262	Enrolling by invitation
Folic acid	Colorectal cancer	II	NCT 02066688	Unknown
Quercetin	Prostate cancer	Not applicable	NCT 01538316	Recruiting
Ginseng	Breast cancer	Not applicable	NCT 03730298	Not yet recruiting
Luteolin	Tongue neoplasm carcinoma	I	NCT 03288298	Not yet recruiting
Epigallocatechin gallate	Small cell carcinoma	I	NCT 01317953	Recruiting
Ginseng	Non-small-cell lung carcinoma Breast and colon cancer	Not applicable I	NCT 03479294 NCT 03407716	Recruiting Not yet recruiting
Tannic acid	Metastatic colorectal cancer	II	NCT 03132025	Not yet recruiting
Hesperidin Tannic acid Anthocyanidin	Breast cancer	Not applicable Not applicable II	NCT 03482401 NCT 02682836 NCT 00041223	Active, not recruiting Recruiting Unknown

The list was obtained from https://clinicaltrials.gov

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VIII. Safety of Phenolic Plant Compounds

Phenolic compounds are generally safe when ingested directly from plant material. Their consumption from food supplements or herbal medicines can cause systemic toxicity. [48] [98] When ingested naturally the body develops mechanisms by which its bioavailability is reduced to avoid toxicity. However, for the pathological treatment, the dose bioavailable must be ensured to avoid failed treatment. On the other hand, the high dose concentration must be limited because it can increase the progress of cancer instead of suppressing it. [90] [99]

IX. The Adverse Effect of Phenolic Compounds

The adverse effects caused by phenolic compounds are mainly because of the following reasons:

- Poor permeability while present as free acids;
- The ability of transforming a healthy cell into cancer cell;
- When given in higher doses it cases toxicity;
- It can lead to infection and unusual inflammatory reaction due to scavenging of reactive oxygen species which is important in many biological processes. [100]

X. Conclusion

Polyphenolic compounds effect on cancers partly due to their effect on various tumors pathway, for instance, epithelial mesenchymal transition (EMT) pathway, apoptosis induction, ROS levels increase. Nevertheless, the successful efficacy of phenolic and polyphenolic compounds also partly due to their modulation of the immune system and other mechanisms in the body. Phenolic compounds play an important role in tumor pathways and are responsible for mediating cancer cell migration and invasive properties which can justify their polyphenolic compounds also play an important role by up-regulating epithelial markers and down-regulating mesenchymal proteins and their antimetastatic effect. Although phenolic compounds possess extensive benefits to health, it is important to mention that they also possess extensive interaction with other ingested drugs and other food materials. They are subjected to vast metabolic degradation. Hence, it is advisable to always use polyphenolic in synergistic mixture because they exert a more and better therapeutic effect when used in a mixture.

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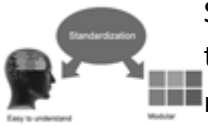


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16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular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

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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

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