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Review Article

PHARMACOLOGY OF TRIPHALA WITH SPECIAL FOCUS ON THEIR CHEMICAL CONSTITUENTS

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ABSTRACT

This review is based on Ayurvedic texts and online scientific databases like PubMed, Google Scholar, Science Direct to study use of scientific research methods in ayurvedic formulation *Triphala*. The following keywords were used: *Triphala, terminalia chebula, terminalia bellerica, Phyllanthus embilica,* chemical constituents, gallic acid, chebulinic acid, and molecular docking to write this review. Studies about *Triphala* and their individual drugs as well as their active compounds were concentrated upon. There are many research works being conducted on *Triphala* and its therapeutic effect. Yet, the need to develop these works to a fully utilisable form for the medical community is not achieved. This review concludes that *Triphala* is a treasure that needs to be further evaluated for the betterment of health globally.

Keywords: *Triphala, Terminalia chebula, Terminalia bellerica, Phyllanthus embilica,* Anticancer, Molecular mechanism, Bioactive compound

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INTRODUCTION

These days, all living organisms are evolving rapidly to survive. Just like the human beings and animals, microbes, including pathogens are evolving to adapt to the continuously changing environment. Pathogens turning into superbugs has become a potential threat while dealing with many ailments. Also, public nowadays are very much concerned about the side effects of various synthetic drugs and are turning to look at natural remedies. Traditional medicines of different countries make use of natural products for curative and preventive purposes [1].

Ayurveda is a traditional Indian system of medicine which has been practiced for over 3000 y. The term Ayurveda in Sanskrit translates into the knowledge of longevity [2]. This system focuses on the prevention of disease as well as curing diseases equally. It gives single and combinations of herbal and mineral drugs for various conditions. The use of such medicines is time-tested and effective, but further research is required to understand their mechanism of action. Various modern scientific tools are extremely helpful in revealing undiscovered facts about ethnomedicine.

Triphala in Sanskrit translates to three fruits. It is a combination of fruits of three plant species (table 2): *Haritaki: Terminalia chebula Retz*. (fig. 1) *Vibhitaki: Terminalia bellerica Roxb*. (fig. 2) *and Amalaki: Emblica officinalis Gaertn. or Phyllanthus emblica Linn* (fig. 3) [3] They are normally taken in equal parts but may vary per condition. It is a widely used ayurvedic medicine and is given in many forms like powder, decoction, ghee etc [3-5]. This combination is used internally as well as externally. It is a well-known *rasayana,* which causes rejuvenation and longevity to individuals of all ages. Charaka Samhitha promotes the use of *Triphala rasayana (Triphala* powder with honey) daily to ensure long and healthy life of an individual [4]. Ashtanga Hridaya mentioned that the use of *Triphala* daily is especially beneficial for the health of the eyes [5].

Recently, a lot of research works have been done on Triphala and it is found to be of great therapeutic potential. It has antimicrobial action, an immunomodulatory effect [6] as well as prebiotic potential [7]. This formulation is effective against cardiovascular diseases [8], tumours [9], various gastrointestinal disorders [10], hypertension [11] and many other diseases.

Studies revealed that *Triphala* is rich in various class of phytochemicals that make this formulation have its unique actions, which place it in an extremely important position among Ayurvedic medicine. Researches found *Triphala* to be effective in the pandemic SARS-CoVid also [12]. Intraperitoneal administration of *Triphala* has radioprotective action against γ-radiation [13].

Many pharmacologically important phytochemicals have been identified from *Triphala* [12]. Individually also, these three plants have been studied to isolate various bioactive compounds to help understand their therapeutic efficacy. The previous studies reported a wide variety of chemical compounds, including phytosterols, alkaloids, phenolics like flavonoids, plant phenols, tannins, and so on [14-16].

MATERIALS AND METHODS

Various studies published in databases like Pubmed, Scopus and Google Scholar were reviewed. Keywords used include: *Triphala, Terminalia chebula, Terminalia bellerica* and *Embilica officinalis,* chemical constituents of *Triphala*. The studies done on *Triphala* and their bioactive compounds were concentrated upon and finally, the selected papers were reviewed.

Ayurvedic view on triphala

Triphala consists of dried fruits of *Haritaki, Vibhitaki* and *Amalaki. Triphala* is considered as *Tridosha shamaka* (pacifying all three humors of human body-*Vata, Pitta* and *Kapha*). It is a very commonly used *Rasayana* (rejuvenator). It is *KaphaPittahara,* cures *Meha, Kushta* and *Vishamajwara.* It promotes good vision, digestion and taste perception. *Triphala* specifically reduces accumulated excess fat and promotes general health and longevity. The ayurvedic properties of these plants are given in table 1.

Table 1: Properties of triphala

S. No.	Drug	Rasa	Guna	Veerya	Vipaka	Karma
1	Haritaki	Madhura, Amla, Katu, Tikta, Kashaya	Laghu Ruksha	Ushna	Madhura	Tridoshahara
2	Vibheetaki	Kashaya	Ruksha, Laghu	Ushna	Madhura	Kaphapittahara
3	Amalaki	Madhura, Amla, Katu, Tikta, Kashaya	Guru, Ruksha, Sheeta	Sheeta	Madhura	Tridoshahara

Table 2: Triphala

S. No.	Drug	Scientific name	Family
1	*Haritaki*	Terminalia chebula	Combretaceae
2	*Vibhitaki*	Terminalia bellerica	Combretaceae
3	*Amalaki*	Embilica officinalis	Euphorbiaceae

Table 3: Major chemical constituents in triphala

S. No.	Chemicals	*T. Chebula*	*T. Bellerica*	*P. Embilica*
1	Alkaloids	Yes	Yes	Yes
2	Flavonoids	Yes	Yes	Yes
3	Steroids	No	No	No
4	Saponins	No	No	No
5	Phenols	Yes	Yes	Yes
6	Tannins	Yes	No	No
7	Glycoside	Yes	No	No
8	Carboxylic acid	No	No	No
9	Sterols	Yes	Yes	Yes
10	Resins	Yes	Yes	Yes
11	Quinines	Yes	Yes	Yes
12	Xanthoproteins	Yes	Yes	No
13	Terpenoids	Yes	Yes	No

Fig. 1: ***Hareetaki***

Fig. 2: ***Vibheetaki***

Fig. 3: ***Amalaki***

Phytochemistry of triphala

Triphala and its individual compounds are extensively studied for their phytochemicals. Identification of chemical constituents help understand various mechanisms by which this combination acts in different conditions (table 3).

Terminalia chebula

Many phytochemicals have been so far identified and studies are still continuing as to their pharmacological actions. Chebulinic acid, Chebulic acid and Gallic acid constitute the main chemical compounds in terminalia chebula.

Other than these a lot of other compounds like Arjunolic acid, Arjugenin, Chebuloside1, Chebuloside2, Chebulic acid, 1,2,3,4,6-Penta-Ogalloyl-β-D-glucose, α-D-Glucopyranose, Chebulagic acid, Eugeniin, 1,2,3,4-tetrakis(3,4,5-trihydroxybenzoate), Corilagin, EuphormisinM3, m-Galloylgallic acid, Punicalagin, Hamamelitannin, Caftaric acid, Gallic acid, Shikimic acid as well as termitomenins A-E have been identified [17, 18].

Terminalia bellerica: The main bioactive compounds found in terminalia bellerica are Glucoside, tannins, gallic acid, ellagic acid, ethyl galate, gallyl glucose and chebulanic acid [19, 20].

Phyllanthus emblica: Main bioactive compounds in this drug include ellagic acid, chebulinic acid and gallic acid.

Many other chemicals like corilagin, chebulagic acid, geraniin, tercatain, methyl chebulagate, dimethyl neochebulagate, Glucogallin, 1,6-bis-O-galloyl-beta-D-glucose, chebulicacid-trimethyl ester, digallic acid etc were also identified by chromatographic methods [21].

Triphala

Some studies have also been done on the specific combination called *Triphala* to identify the main compounds as well as for standardization purposes. The compounds confirmed in *Triphala* are: gallic acid, chebulagic acid and chebulinic acid, tannic acid, syringic acid and epicatechin along with ascorbic acid [22, 23].

Structures of some important chemicals in *Triphala*

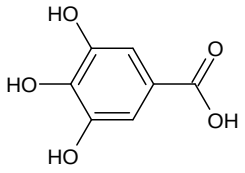

Fig. 1: Gallic acid

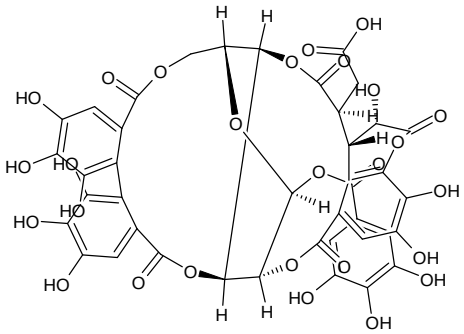

Fig. 2: Chebulagic acid

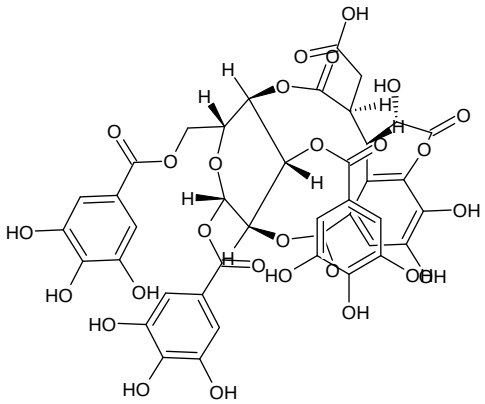

Fig. 3: Chebulinic acid

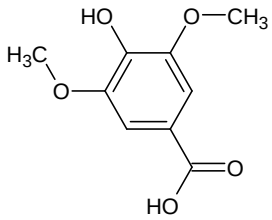

Fig. 4: Syringic acid

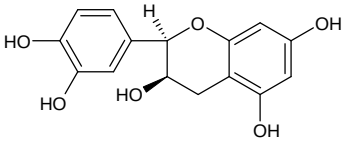

Fig. 5: Epicatechin

Gallic acid

It is a well-known plant metabolite. It is the conjugate acid of gallate and a phenolic compound. It is a trihydroxybenzoic acid. It can exist in free-state or as the tannin-constituent: gallotannin. *Triphala* and its individual drugs all contain gallic acid along with its various derivatives. This molecule is an active agent against colitis as proven in mouse-studies. This effect was proven to be via inhibition of NFkB and activating STAT3 in animal models [24]. It was found effective in the treatment of gouty arthritis in mice model. It acts by suppressing ROS generation, thus limiting NLRP3 inflammasome activation and pyroptosis [26]. The toxicity were studied systematically and concluded this to be safe on administration even in high dosages [27].

Chebulagic acid

Low dose administration of this drug in experimental mice was found to inhibit Vascular endothelial growth factor A and thereby angiogenesis [28]. Research found it to pocess antidiabetic activity. It helped to normalize carbohydrate metabolizing enzymes like PPARγ and GLUT4 [29]. Chebulagic, Chebulinic, and Gallic acids, are found to have anti-inflammatory action [30]. Chebulagic acid showed potent activity in both cellular and animal models of human enterovirus 71 [31]. This compound was found to be anticancerous. It showed antiproliferative action as well as it inhibited enzymes involved in the pathology that is COX and 5-LOX [32].

Chebulinic acid

Among 1033 natural products screened, chebulinic acid was found to strongly inhibit the hydrolysis of 6,8-difluoro-4-methylumbelliferyl phosphate by protein phosphatase-1 catalytic subunit beta and demonstrated potent antiadipogenic effects in 3T3-L1 preadipocytes. Thus its action in obesity is studied [33]. Chebulinic acid from *Triphala* was found to be a potent antitumour agent, probably acting via PI3K/AKT and MAPK/ERK pathways [34].

Syringic acid

Syringic acid is a compound that is a proven anti-asthmatic agent by its anti-inflammatory action in mice models. Treatment with this drug found reduction in eosinophils and neutrophils as well as in interleukins 4,5 and 13, along with a marked reduction of TNF [25]. This phenolic compound is synthesized in plants through the shikmic acid pathway [35]. This compound also showed promising hepatoprotective activity in experimental mice models [36, 37].

Tannic acid

It was widely used for therapeutic purposes like gastrointestinal diseases, topically for burns and even used in barium enemas for clear x ray imaging. However, due to adverse health reactions, these are discontinued [38]. It is moderately toxic on inhalation. In smaller doses, it is safe [39].

Epicatechin

It was found effective against CVD in thernoneutrally housed wistar rats models. Improved vasodilation, lessened mitochondrial respiration [40]. Epicatechin exerted inhibitions on the activity of phospholipases A2 present in the venom of Bothrops alternatus. This study suggested to the effect of epicatechin as an adjuvant therapy for snake venom [41]. While studying the ROS scavenging activity, the chemical reactivity of (-)-epicatechin quinone was found to be mainly residing in its B-ring [42].

Studies on triphala

There are many studies done on *Triphala* which proved its therapeutic actions and multiple target effect. It is mostly used in

gastrointestinal diseases and for rejuvenative purposes. These days various uses of *Triphala* both in Traditional medicines lika Ayurveda and in folklore are being explored with modern scientific research methods and many give positive results. This specific combination has been scientifically studied for its various actions like anti-ulcer, antioxidant activity, anti-inflammatory, immunomodulatory, antimicrobial, antihypertensive, antitumor, chemopreventing, and radiopreventive effects, prebiotic effects, promoting dental health and so on.

Chebulagic and Chebulinic acids, along with Gallic acid, are found to have anti-inflammatory action. These two compounds, which are pharmacologically important components of *Triphala*, are evident inhibitors of p38, ERK and NFkB activities, thereby protecting retinal capillaries from angigenic and inflammatory damages [30]. Recent advances in computational tools have helped in identifying the exact molecular action of *Triphala* in particular disease pathologies [43].

In silico approaches showed that Phyllanthus embilica had chemicals that are antidiabetic in action [44]. Among about 16 compounds from *Terminalia chebula*, 3 showed a good binding affinity with enzymes involved in diabetes management. Ellagic acid was found to have the greatest affinity to bind with enzymes α-amylase, β-glucosidase and α-glucosidase. This study supports its antidiabetic activity [45]. *Terminalia chebula* extract was found to be an effective inhibitor of AChE and BChE. The chemical constituent in it, namely methyl N(N-benzyloxycarbonyl-β-l-aspartyl)-β-d-glucosaminide was found to be the most potent compound through docking studies [46].

The main constituents of the drug *T. bellerica* were analysed with drug targets involved in pathology of schizophrenic disorder. Among all constituents, β-sitosterol, ellagic acid, and quercetin showed high binding affinity towards all potential targets included. The study concluded that *T. bellerica* has great potential as a natural antipsychotic drug source [47].

Molecular docking studies also proved that bioactive molecules from Phyllanthus embilica were also proven as potent inhibitors of AChE and BChE [48]. The biologically active constituents of T. *bellerica,* including Anolignan B, Gallic acid, Termilignan and Thannilignan, were evaluated by molecular docking. Among all the compounds, Anolignan B was considered as the most effective compound inhibiting estrogen receptor α. The study showed active bio components from *Terminalia bellerica* having promising anticancer activity [49].

In silico studies also suggest therapeutic action of *Triphala* against COVID19. Chebulinic acid has good binding affinity with the formation of 10 hydrogen bonds. Most of the active chemical constituents of *Triphala* were found to form two or more hydrogen bonds with the receptor-binding protein of SARS-CoV-2 Spike Glycoprotein [50].

The action of *Triphala* on CYP2E1 were analysed by molecular docking methods. Here important phytochemical constituents of *Triphala* such as chebulic acid, ellagic acid, epicatechin and ascorbic acid were docked with the said target protein ie. CYP2E1. The research gave very promising inhibiting efficacy of *Triphala* in terms of binding affinity towards the chosen target. The study suggested that in future, these molecules can be used to overcome cancer in association with oxidative stress emerging from the abnormally increased activity of CYP2E1 [51].

The mechanism of action by *Triphala* on cardiovascular diseases and cerebrovascular diseases with focus on their multiple targets were analysed. Over 130 compounds were evaluated, out of which 10, linked to more than three genes. The anti-angiogenic effect was mediated by the combined effect of punicalagin and chebulagic acid [52]. *Triphala* bioactives target 39 proteins which are expressed in 45 different tissues that come under 11 tissue types. The results revealed interaction potential towards multiple targets that cover almost all tissues of the body. This gives a reason as to why *Triphala* is considered as *rasayana* in Ayurvedic medicine [53]. While considering the anticancer effect of *Triphala*, the Bioactive-target-target class network of *Triphala* showed the involvement of 19 cancer related targets. Network pharmacology approaches point out that *Triphala* could broadly mediate the proliferation and apoptosis through different signaling pathways, mainly including PI3K, NF-kB and others [54].

Bioactive compounds from *Triphala* showed potent action against PLA2 both *in vitro* and *in silico.* An important compound called "Morin (3,5,7,2',5'-Pentahydroxyflavone) 9,10 anthraquinone" was proven as an efficient binder inhibiting the target. This work showed that *Triphala* contains various probable leads in oncological therapy and other inflammatory diseases [55].

Further scopes

Even though there are many evidences pointing out to the multiple target action of *Triphala* that strongly supports its use in ethnomedicine, very few have reached a state of solid structured and recorded research studies that can be quickly made use of for the benefit of health advancements. There are very few clinical studies available about the action of *Triphala.* Those are themselves mostly limited to topical applications, mainly in dentistry. The pre-clinical studies have given evidence to a very wider action and they still remain unexplored fully.

The exact pathways and molecular mechanisms that have been identified should be further probed to identify and/or synthesize structurally and pharmacologically similar active molecules that can further be studied for drug-likeness and eventually developed into new drugs. There have been many research studies suggestive of the positive effect of *Triphala* on diseases that are difficult to treat, including various cancers, neurological diseases, cardiovascular diseases, diabetic retinopathy etc [56-61]. Such studies need to be carefully analysed and further developed to successfully incorporate *Triphala* or its active compounds for practical therapeutic purposes.

CONCLUSION

Drug discovery has been a very time-consuming process until computational tools were employed to aid the same. Traditional medicines have potent multi-targeted actions that are not yet discovered and/or explained scientifically. Computational tools can help to identify the potential drug candidates from Ayurvedic medicines and help develop drugs for various diseases. The mechanism of action of different Ayurvedic medicines could be explained by such approaches and thus help in the scientific validation of traditional medicine. New potential drug candidates can be identified from safe, time-tested formulations and may be easily developed further. *Triphala* and its studies provides a good example on how such approaches impart scientific evidence and help improve medical science as a whole.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016 Apr 29;21(5):559. doi: 10.3390/molecules21050559, PMID 27136524, PMCID PMC6273146.
2. Puranik A, Patwardhan B. Ayurveda and metabolic diseases: the whole is greater than the sum of the parts. 2012. p. 443-56. doi: 10.1016/B978-0-12-385083-6.00035-8.
3. Shastri PP, Sharangadhara Samhita of Sharangadhara, Sanskrit text with Adhamalla's Dipika commentary and Kashiram's Gudartha-Dipika commentary, Madhyamakhanda, Ch 6; 2020. p. 179.
4. Sharma PV. Charaka samhita part 2. Chaukambha Orientalia Varanasi. 2011;24:1.3/41-42.
5. Vahata SAN. Ashtavaidyan vaidyamadhom cheriya narayanan namboodiri math ashtanga hridaya samhitha with sasilekha

commentary of Indu. 2nd ed. Varanasi, India: Chowkambha Krishnadas Academy; 2019. p. 513.
6. Belapurkar P, Goyal P, Tiwari Barua P. Immunomodulatory effects of triphala and its individual constituents: a review. Indian J Pharm Sci. 2014 Nov-Dec;76(6):467-75. PMID 25593379, PMCID PMC4293677.
7. Peterson CT, Pourang A, Dhaliwal S, Kohn JN, Uchitel S, Singh H. Modulatory effects of *Triphala* and *Manjistha* dietary supplementation on human gut microbiota: A double-blind, randomized, placebo-controlled pilot study. J Altern Complement Med. 2020 Nov;26(11):1015-24. doi: 10.1089/acm.2020.0148. PMID 32955913.
8. Wang W, Liu T, Yang L, Ma Y, Dou F, Shi L. Study on the multi-targets mechanism of triphala on cardio-cerebral vascular diseases based on network pharmacology. Biomed Pharmacother. 2019 Aug;116:108994. doi: 10.1016/j.biopha.2019.108994. PMID 31112872.
9. Shi Y, Sahu RP, Srivastava SK. Triphala inhibits both *in vitro* and *in vivo* xenograft growth of pancreatic tumor cells by inducing apoptosis. BMC Cancer. 2008 Oct 10;8:294. doi: 10.1186/1471-2407-8-294, PMID 18847491, PMCID PMC2576337.
10. Nariya M, Shukla V, Jain S, Ravishankar B. Comparison of enteroprotective efficacy of triphala formulations (Indian Herbal Drug) on methotrexate-induced small intestinal damage in rats. Phytother Res. 2009 Aug;23(8):1092-8. doi: 10.1002/ptr.2744, PMID 19170156.
11. Mashyal P, Bhargav H, Raghuram N. Safety and usefulness of Laghu shankha prakshalana in patients with essential hypertension: A self controlled clinical study. J Ayurveda Integr Med. 2014 Oct-Dec;5(4):227-35. doi: 10.4103/0975-9476.131724, PMID 25624697, PMCID PMC4296435.
12. Rudrapal M, Celik I, Khan J, Ansari MA, Alomary MN, Yadav R. Identification of bioactive molecules from Triphala (Ayurvedic herbal formulation) as potential inhibitors of SARS-CoV-2 main protease (Mpro) through computational investigations. J King Saud Univ Sci. 2022 Apr;34(3):101826. doi: 10.1016/j.jksus.2022.101826. PMID 35035181, PMCID PMC8744360.
13. Jagetia GC, Baliga MS, Malagi KJ, Sethukumar Kamath M. The evaluation of the radioprotective effect of Triphala (an ayurvedic rejuvenating drug) in the mice exposed to gamma-radiation. Phytomedicine. 2002 Mar;9(2):99-108. doi: 10.1078/0944-7113-00095, PMID 11995956.
14. Mohanasundaram S, Rangarajan N, Sampath V, Porkodi K, Pennarasi M. GC-MS and HPLC analysis of antiglycogenolytic and glycogenic compounds in kaempferol 3-O–gentiobioside containing Senna alata L. leaves in experimental rats. Translational. Metab Syndr Research. 2021;4:10-7.
15. Vemuri PK, Dronavalli L, Nayakudugari P, Kunta A, Challagulla R. Phytochemical analysis and biochemical characterization f terminalia chebula extracts for its medicinal use. Biomed Pharmacol J. 2019;12(3):1525-9. doi: 10.13005/bpj/1783.
16. Wu L, Zhang Q, Liang W, Ma Y, Niu L, Zhang L. Phytochemical analysis using UPLC-MSn combined with network pharmacology approaches to explore the biomarkers for the quality control of the anticancer tannin fraction of Phyllanthus emblica L. habitat in Nepal. Evid Based Complement Alternat Med. 2021. doi: 10.1155/2021/6623791, PMID 33833816.
17. Li K, Han X, Li R, Xu Z, Pan T, Liu J. Composition, antivirulence activity, and active property distribution of the fruit of terminalia chebula retz. J Food Sci. 2019 Jul;84(7):1721-9. doi: 10.1111/1750-3841.14655. PMID 31206192.
18. Zhang XR, Zhu HT, Wang D, Yang Z, Yang CR, Zhang YJ, Termitomenins AE. Five new lignans from Terminalia chebula var. tomentella (Kurz) C. B. Clarke Fitoterapia. 2020;143:104571. doi: 10.1016/j.fitote.2020.104571. PMID 32209392.
19. Kumar N, Khurana SM. Phytochemistry and medicinal potential of the Terminalia bellirica Roxb. (Bahera). Indian J Nat Prod Resour. 2018;9(2):97-107.
20. Makihara H, Koike Y, Ohta M, Horiguchi Babamoto E, Tsubata M, Kinoshita K. Gallic acid, the active ingredient of terminalia bellirica, enhances adipocyte differentiation and adiponectin secretion. Biol Pharm Bull. 2016;39(7):1137-43. doi: 10.1248/bpb.b16-00064. PMID 27374289.
21. Yang F, Yaseen A, Chen B, Li F, Wang L, Hu W. Chemical constituents from the fruits of Phyllanthus emblica L. Biochem Syst Ecol. 2020;92:104122. doi: 10.1016/j.bse.2020.104122.
22. Pawar V, Lahorkar P, Anantha Narayana DB. Development of a RP-HPLC method for analysis of Triphala Curna and its applicability to test variations in Triphala Curna preparations. Indian J Pharm Sci. 2009 Jul;71(4):382-6. doi: 10.4103/0250-474X.57286, PMID 20502543, PMCID PMC2865809.
23. Mohanasundaram S, Doss VA, Maddisetty P, Magesh R, Sivakumar K, Subathra M. Pharmacological analysis of hydroethanolic extract of Senna alata (L.) for *in vitro* free radical scavenging and cytotoxic activities against Hep G2 cancer cell line. Pak J Pharm Sci. 2019;32(3):931-4.
24. Pandurangan AK, Mohebali N, Esa NM, Looi CY, Ismail S, Saadatdoust Z. Gallic acid suppresses inflammation in dextran sodium sulfate-induced colitis in mice: possible mechanisms. Int Immunopharmacol. 2015 Oct;28(2):1034-43. doi: 10.1016/j.intimp.2015.08.019. PMID 26319951.
25. Li Y, Zhang L, Wang X, Wu W, Qin R. Effect of syringic acid on antioxidant biomarkers and associated inflammatory markers in mice model of asthma. Drug Dev Res. 2019 Mar;80(2):253-61. doi: 10.1002/ddr.21487. PMID 30474283.
26. Lin Y, Luo T, Weng A, Huang X, Yao Y, Fu Z. Gallic acid alleviates gouty arthritis by inhibiting NLRP3 inflammasome activation and pyroptosis through enhancing Nrf2 signaling. Front Immunol. 2020 Dec 7;11:580593. doi: 10.3389/fimmu.2020.580593, PMID 33365024, PMCID PMC7750458.
27. Variya BC, Bakrania AK, Madan P, Patel SS. Acute and 28-days repeated dose sub-acute toxicity study of gallic acid in albino mice. Regul Toxicol Pharmacol. 2019 Feb;101:71-8. doi: 10.1016/j.yrtph.2018.11.010. PMID 30465803.
28. Lu K, Basu S. The natural compound chebulagic acid inhibits vascular endothelial growth factor a mediated regulation of endothelial cell functions. Sci Rep. 2015 Apr 10;5:9642. doi: 10.1038/srep09642, PMID 25859636, PMCID PMC4819393.
29. Vasu G, Sundaram R, Muthu K. Chebulagic acid attenuates HFD/streptozotocin induced impaired glucose metabolism and insulin resistance via up regulations of PPAR γ and GLUT 4 in type 2 diabetic rats. Toxicol Mech Methods. 2022 Mar;32(3):159-70. doi: 10.1080/15376516.2021.1976333. PMID 34470562.
30. Shanmuganathan S, Angayarkanni N. Chebulagic acid chebulinic acid and gallic acid, the active principles of Triphala, inhibit TNFα induced pro-angiogenic and pro-inflammatory activities in retinal capillary endothelial cells by inhibiting p38, ERK and NFkB phosphorylation. Vasc Pharmacol. 2018 Sep;108:23-35. doi: 10.1016/j.vph.2018.04.005. PMID 29678603.
31. Yang Y, Xiu J, Liu J, Zhang L, Li X, Xu Y. Chebulagic acid, a hydrolyzable tannin, exhibited antiviral activity *in vitro* and *in vivo* against human enterovirus 71. Int J Mol Sci. 2013 May 3;14(5):9618-27. doi: 10.3390/ijms14059618. Erratum in: Int J Mol Sci. PMID: 23644889, PMC3676802.
32. Mohanasundaram S, Ramirez Asis E, Quispe Talla A, Bhatt MW, Shabaz M. Experimental replacement of hops by mango in beer: production and comparison of total phenolics, flavonoids, minerals, carbohydrates, proteins and toxic substances. Int J Syst Assur Eng Manag. 2022;13(S1):132-45. doi: 10.1007/s13198-021-01308-3.
33. Kim J, Ahn D, Chung SJ. Chebulinic acid suppresses adipogenesis in 3T3-L1 preadipocytes by inhibiting PPP1CB activity. Int J Mol Sci. 2022 Jan 13;23(2):865. doi: 10.3390/ijms23020865, PMID 35055051, PMCID PMC8775935.
34. Wang M, Li Y, Hu X. Chebulinic acid derived from triphala is a promising antitumour agent in human colorectal carcinoma cell lines. BMC Complement Altern Med. 2018 Dec 27;18(1):342. doi: 10.1186/s12906-018-2412-5, PMID 30587184, PMCID PMC6307174.
35. Srinivasulu C, Ramgopal M, Ramanjaneyulu G, Anuradha CM, Suresh Kumar C. Syringic acid (SA)– a review of its occurrence, biosynthesis, pharmacological and industrial importance. Biomed Pharmacother. 2018 Dec;108:547-57. doi: 10.1016/j.biopha.2018.09.069. PMID 30243088.

36. Mohanasundaram S, Rangarajan N, Sampath V, Porkodi K, Dass Prakash MV, Monicka N. GC-MS identification of anti-inflammatory and anticancer metabolites in edible milky white mushroom (Calocybe indica) against human breast cancer (MCF-7) cells. Res J Pharm Technol. 2021;14(8):4300-6.
37. Rangarajan N, Sampath, Dass Prakash M, Mohanasundaram S. UV Spectrophotometry and FTIR analysis of phenolic compounds with antioxidant potentials in glycyrrhiza glabra and zingiber officinale. IJRPS 2021;12(1):877-83. doi: 10.26452/ijrps.v12i1.4215.
38. Robles H. Tannic acid. Encyclopedia of toxicology. 3rd ed. Wexler P, editor. Academic Press; 2014. p. 474-5. doi: 10.1016/B978-0-12-386454-3.00542-X.
39. Barium sulfate. Meyler's side effects of drugs. 16th ed Aronson JK, editor. Elsevier, 2016. p. 827-9. doi: 10.1016/B978-0-444-53717-1.00350-4.
40. Chun JH, Henckel MM, Knaub LA, Hull SE, Pott GB, Walker LA. (-)-Epicatechin improves vasoreactivity and mitochondrial respiration in thermoneutral-housed wistar rat vasculature. Nutrients. 2022 Mar 5;14(5):1097. doi: 10.3390/nu14051097, PMID 35268072, PMCID PMC8912787.
41. Rangarajan N, Sangeetha R, Mohanasundaram S, Sampath, Porkodi K, Dass Prakash MV. Additive inhibitory effect of the peels of Citrus limon and Citrus sinensis against amylase and glucosidase activity. IJRPS 2020;11(4):6876-80. doi: 10.26452/ijrps.v11i4.3661.
42. Zhang M, Vervoort L, Moalin M, Mommers A, Douny C, den Hartog GJM. The chemical reactivity of (-)-epicatechin quinone mainly resides in its B-ring. Free Radic Biol Med. 2018 Aug 20;124:31-9. doi: 10.1016/j.freeradbiomed.2018.05.087. PMID 29859347.
43. Wang Q, Sivakumar K, Mohanasundaram S. Impacts of extrusion processing on food nutritional components. Int J Syst Assur Eng Manag. 2022;13(S1):364-74. doi: 10.1007/s13198-021-01422-2.
44. Chowdhury HU, Adnan MD, Oh KK, Cho DH. Decrypting molecular mechanism insight of phyllanthus emblica L. fruit in the treatment of type 2 diabetes mellitus by network pharmacology, Phytomedicine. Plus. 2021;1(4):100144. doi: 10.1016/j.phyplu.2021.100144.
45. Bansode TS, Salalkar BK. Strategies in the design of antidiabetic drugs from Terminalia chebula using *in silico* and *in vitro* approach. Micromedicine. 2016;4(2):60-7. doi: 10.5281/zenodo.167869.
46. Rajmohamed MA, Natarajan S, Palanisamy P, Abdulkader AM, Govindaraju A. Antioxidant and cholinesterase inhibitory activities of ethyl acetate extract of terminalia chebula: cell-free *in vitro* and *in silico* studies. Pharmacogn Mag. 2017;13(Suppl 3):S437-45. doi: 10.4103/pm.pm_57_17. PMID 29142396.
47. Fei LC, Gaurav A, Al-Nema M. *In silico* investigations on the probable macromolecular drug targets involved in the anti-schizophrenia activity of terminalia bellerica. Lett Org Chem. 2021;19(1):83-92. doi: 10.2174/1570178618666210315152721.
48. Meghana Y, Srikanth J. *Ex vivo*, *in vitro* and *in silico* neuroprotective activity of selected traditional medicinal plants-a reverse pharmacological approach. Int J Pharm Res. 2021.
49. Majumder M, Khanam T, Rahaman M, Rahimul M, Hossain TN, Chakrabarty N. Anticancer potential of isolated phytochemicals from terminalia bellerica against breast cancer: *in silico* molecular docking approach. World J Pharm Res. 2017 Feb 19;6(4):1763-71.
50. Khan SL, Siddiqui FA, Shaikh MS, Nema NV, Shaikh AA. Discovery of potential inhibitors of the receptor-binding domain (RBD) of pandemic disease-causing SARS-CoV-2 spike glycoprotein from triphala through molecular docking. Current Chinese Chemistry. 2021;2(1). doi: 10.2174/2666001601666210322121802.
51. Unnisa A, Khan SL, Sheikh FAH, Mahefooz S, Kazi AA, Siddiqui FA. *In silico* inhibitory potential of triphala constituents against cytochrome P450 2E1 for the prevention of thioacetamide-induced hepatotoxicity. J Pharm Res Int. 2021:367-75. doi: 10.9734/jpri/2021/v33i43A32499.
52. Abhinand CS, Athira PA, Soumya SJ, Sudhakaran PR. Multiple targets directed multiple ligands: an *in silico* and *in vitro* approach to evaluating the effect of triphala on angiogenesis. Biomolecules. 2020 Jan 23;10(2):177. doi: 10.3390/biom10020177, PMID 31979409, PMCID PMC7072423.
53. Chandran U, Mehendale N, Patil S, Chaguturu R, Patwardhan B. Network pharmacology. Innov Approaches Drug Discov. 2017:127-64. doi: 10.1016/B978-0-12-801814-9.00005-2, PMCID PMC7148629.
54. Zhao Y, Wang M, Tsering J, Li H, Li S, Li Y. An integrated study on the antitumor effect and mechanism of Triphala against gynecological cancers based on network pharmacological prediction and *in vitro* experimental validation. Integr Cancer Ther. 2018;17(3):894-901. doi: 10.1177/1534735418774410, PMID 29742928.
55. Murthy Malladi S, Sastry Yarla N, Kumar Pandey D. Enzyme inhibition activity both *in vitro* and *in silico* screening of triphala plant extracts on phospholipase A2. Int J Pharm Investig. 2021;11(2):158-64, doi: 10.5530/ijpi.2021.2.29.
56. Chainani SH, Siddana S, Reddy C, Manjunathappa TH, Manjunath M, Rudraswamy S. Antiplaque and antigingivitis efficacy of triphala and chlorhexidine mouthrinse among schoolchildren– a cross-over, double-blind, randomised controlled trial. Oral Health Prev Dent. 2014;12(3):209-17. doi: 10.3290/j.ohpd.a32674. PMID 25197734.
57. Srinagesh J, Pushpanjali K. Assessment of antibacterial efficacy of triphala against mutans streptococci: a randomised control trial. Oral Health Prev Dent. 2011;9(4):387-93. PMID 22238738.
58. Pradeep AR, Suke DK, Martande SS, Singh SP, Nagpal K, Naik SB. Triphala, a new herbal mouthwash for the treatment of gingivitis: a randomized controlled clinical trial. J Periodontol. 2016 Nov;87(11):1352-9. doi: 10.1902/jop.2016.130406. Epub 2016 Jul 21. PMID: 27442086.
59. Victor Arokia Doss VA, Prasad Maddisetty P, Mohanasundaram S. Biological active compounds with various medicinal values of Strychnos nux-vomica–a pharmacological summary. J Global Trends Pharm Sci. 2016;7(1):3044-7.
60. Ning W, Li S, Tsering J, Ma Y, Li H, Ma Y, Ogbuehi AC, Pan H, Li H, Hu S, Liu X, Deng Y, Zhang J, Hu X. Protective effect of riphala against oxidative stress-induced neurotoxicity. BiomMed Res Int. 2021 Apr 7;2021:6674988. doi: 10.1155/2021/6674988, PMID: 33898626, PMCID: PMC8052154.
61. Sahragard A, Alavi Z, Abolhassanzadeh Z, Moein M, Mohammadi Bardbori A, Omidi M, Zarshenas MM. Assessment of the cytotoxic activity of riphala: A semisolid traditional formulation on HepG2 cancer cell line. BiomMed Res Int. 2021 Aug 11;2021:6689568. doi: 10.1155/2021/6689568, PMID: 34471640, PMCID: PMC8405286.