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A REVIEW STUDY ON THE PHARMACOLOGICAL EFFECTS AND MECHANISM OF ACTION OF TANNINS

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ABSTRACT

Tannins are considered as valuable plant secondary metabolites that have a variety of health benefits. They possess potentially many pharmacological properties for which they are used in the versatile fields of treatment. Tannins are now considered as an indispensable component with external and internal effects in a variety of nutraceuticals, pharmaceuticals, and medicinal preparations. The external treatments of tannin are the treatment of skin inflammation and injuries and may prevent the inception of many chronic diseases. On the other hand, internally tannin compounds may produce effects on the gastrointestinal tract including antioxidant, free radical scavenging, antimicrobial, antiviral, anti-mutagenic, anti-carcinogen, anthelmintic, hepatoprotective effects, an inhibitor of the harmful pro-oxidative enzyme, and anti-nutrient effects. Moreover, different tannins have chemopreventive effects on the breast, oral cavity, prostate glands, stomach, and skin cancer. They also show astringent and antiseptic properties happened by binding, precipitating, or shrinking with different protein molecules. A number of tannins are available in the market as an unabsorbable and absorbable form having potent and extended pharmacological activities, higher safety profile, low toxicity, and cost-effectiveness. Although many of the above characteristics of tannins have been studied theoretically and practically but still there remains a scarcity of systematic knowledge regarding pharmacological effects and their mechanisms of action. So, the present review is designed to focus on the pharmacological effects and mechanism of action of tannin and its congeners along with slightly lighting on other significant properties.

KEYWORDS: External treatment, internal treatment, chronic diseases, antioxidant, pro oxidative enzyme, chemo preventive effects, astringent, un-absorbable and absorbable form, etc.

INTRODUCTION

Tannins are polyphenolic secondary metabolites found in higher plants. They are both galloyl esters and their derivatives, wherein galloyl moieties or their derivatives are connected to a variety of polyol, catechin,[7] and triterpenoid cores, or they are oligomeric and polymeric proanthocyanidins that may possess distinct inter flavanyl coupling and substitution patterns.[1] Classically tannins are classified on the basis of their resistance to hydrolysis by hot water or tannases. Hydrolysable tannins encompass polyesters of gallic and hexahydroxydiphenic acid (gallotannins and ellagitannins, respectively) whereas condensed tannins include oligomers and polymers composed of flavan-3-ol nuclei (proanthocyanidins).[2] According to the new style, tannins are alienated based on their structural characteristics [19] into four major groups including gallotannins, ellagitannins, complex tannins, and condensed tannins. Another principal classification of tannins is based on the chemical structure's stability. In this way, tannins and polyphenols related to tannins can be categorized as polyphenols of constant chemical structure (Type A) and polyphenols of variable composition (Type B). Characterization of any target molecule's biological and pharmacological features, as well as their methods of action, require constancy in chemical structure and composition.[3] So the present review study is designed to focus on the pharmacological and biological effects and mechanisms of action of tannin and its congeners along with slightly lighting on other significant properties.

Pharmacological Spectra of Tannins

The range or wideness of activities of any substances against illness is known as the pharmacological activity spectra of that substances and the same of tannins are very wide consisting of external and internal effects. The external treatments of tannin are the treatment of skin inflammation and injuries and may prevent the inception of many chronic diseases.[4] The biological and pharmacological effects of tannins have been studied using various in vitro or in vivo models. However, there

still remains a scarcity of at a glance systematic arrangement of pharmacological activities and their mechanisms of action of the same. Internally they may exert pharmacological effects in two different ways. Firstly, it is an unabsorbable, complex structure having binding properties that may produce effects on the gastrointestinal tract including antioxidant, free radical scavenging, antimicrobial, antiviral, anti-mutagenic, anti-carcinogenesis, anthelmintic, hepatoprotective effects, harmful pro-oxidative enzyme inhibitor, and anti-nutrient effects inhibitor. Numerous other studies with different cell cultures have reported chemopreventive effects of tannins on breast, oral cavity, prostate glands, stomach, and skin cancer. [14] They also possess astringent and antiseptic properties that exerted by binding, precipitating or shrinking different superficial protein molecules of human beings. On the other hand, they are shown to act as absorbable low molecular weight tannins and metabolites from colonic fermentation of tannins producing systemic effects in various living organ systems. [4,5] The above-mentioned subject matters relating to the pharmacological effect and their modes and mechanisms of action are described separately below:

Antioxidant and free radical scavenging properties of tannins

Different molecules belonging to tannins inhibit lipid peroxidation and able to hunt cellular and molecular free radicals, especially in pro-oxidant states. These free radical-scavenging properties with other activities, largely depend on structures and intensity of polymerization.[5] Ellagitannin pedunculagin, possessing two hexahydroxy diphenyl groups and complex tannins including epigallocatechin gallate is proved to inhibit lipid peroxidation most potently. Several hydrolysable tannins eg pentagalloyl glucose and geraniin were shown to inhibit xanthin– xanthine oxidase caused lipid peroxidation. Extremely condensed kaki-tannin significantly inhibited the lipid auto-peroxidation. Further, it was estimated that kaki-tannin was 100-times more potent than the others as an inhibitor of auto-oxidation or induced oxidation. Another study discovered that various tannins have a seven-fold increase in radical scavenging capability as the degree of polymerization of proanthocyanidin increases.[16] In addition, potent *in vitro* scavenging effects were demonstrated also in the 2,2-diphenyl-1- picrylhydrazyl (DPPH) test by the hydrolysable pentagalloyl-glucose, tellimagrandins I and II, pedunculagin, isoterchebin, mallotusinic acid, geraniin, and chebulinic acid, although the effects of the maximum of low molecular weight tannins, were found very low quantity.[5]

Antimicrobial activity

Several dimeric tannins exhibit antibacterial activity[6] against methicillin-resistant *Staphylococcus aureus* and reduced the resistance to oxacillin. Tannins appear to exert these effects in varieties of methods, including inhibition of extracellular microbial enzymes,[8,12] deprivation of microbial growth substrates, or direct action on microbial metabolism via suppression of oxidative phosphorylation.[9] Tannins' antibacterial effect may be mediated by their ability to complex metal ions in the bacterial growth environment.[3] Tannins were proven to have antibacterial activity against a variety of human gastrointestinal pathogens. Ellagitannins have been shown to be potent inhibitors of *Staphylococcus* bacteria, *Candida albicans*, and *Campylobacter jejuni*.[4] The Catechins have been tested for antibacterial activity against *Helicobacter pylori*. Among (+) catechin (C), (−) epicatechin (EC), (−) epigallocatechin (EGC), ECG, and EGCG; only EGCG and ECG showed antibacterial activity against *H. pylori* at the 100 μg/mL concentration level.[10] Catechin, on the other hand, has been demonstrated to suppress the development of *H. pylori* and *E. coli* in a dose and time-dependent manner in another study.[11] Funatogawa and coworkers described that hydrolysable tannins and acid-treated hydrolysable tannins demonstrated promising activity. The activity of hydrolysable tannin monomers was higher than that of oligomers and catechins. With a few exceptions, procyanidins showed minimal antibacterial activity against *H. pylori*. The above activities of hydrolysable tannins are very important and may due to their higher water solubility. Moreover, acid-treatment hardly affected the antibacterial activity of hydrolysable tannins *in vitro*, suggesting working in the acidic gastric environment. Gallotannins were described as active inhibitors of water-insoluble glucan synthesis developing bactericidal activity against *Streptococcus mutans*, *S. salivarius*, and *Actinomyces viscosus*.[14] Another study showed that the complex tannin the asinensin A caused a noticeable reduction in MIC values of oxacillin for the MRSA strains. Oxacillin, in the presence of the asinensin A completely inhibits cell growth over 10 hours. This type of reduction of resistance to oxacillin was observed with the tea polyphenol (-)-epicatechingallate, procyanidins B3 and B4 and for the hydrolysable tannins tellimagrandin I, rugosin B, and corilagin. The asinensin A also reduces the MIC values of the other β-lactams, penicillin G, ampicillin, streptomycin, etc. Cranberry juice possesses proanthocyanidins with special antimicrobial effects causing suppression of *E. coli* adherence to human uroepithelium,[20] and it is for the repetition of a catechin unit with one or more A-type linkages of proanthocyanidins.

Antiviral activity

Natural and synthetic tannins manifest activity against a large spectrum[17,18] of viruses including enteroviruses, caliciviruses, rotavirus, influenza virus A, rhabdo-(vesicular stomatitis virus), paramyxoviruses, human immunodeficiency virus, herpes simplex virus,[13,16] and adenoviruses. Antiviral mechanism of action of tannins includes inhibition of the virus adsorption, penetration, adsorption/penetration into the nucleus, and inhibition into the viral reverse transcription. These substances may able to interact with multiple viral targets which have been demonstrated by radiolabelled virus particles of

Herpes simplex. This reveals the antiviral effects of hydrolysable and galloylated condensed tannins were due to inhibition of virus adsorption. [22] The quantity of galloyl or hexahydroxydiphenoyl groups in hydrolysable tannins determined their antiherpetic activity, whereas condensed tannins' antiherpetic activity increased with the degree of condensation.[23] Potent anti-human immune-deficiency virus (HIV) activities partly mediated by adsorption inhibition were found for the dimeric ellagitannins oenothein B, coriariin A, and agrimoniin. The inhibition in adsorption could be due to its binding to components of the viral envelope, preventing viral attachment and penetration of the plasma membrane.[24] The ellagitannin casuarinin was also found to possess anti-herpes virus activity in inhibiting viral attachment to cells and viral penetration, and also disturbing the late event(s) of infection.[25] Other hydrolysable tannins, chebulagic acid, and punicalagin.[15] were effective in repealing infection caused by human cytomegalovirus (HCMV), hepatitis C virus (HCV), dengue virus (DENV), measles virus (MV), and respiratory syncytial virus (RSV) at micromolar concentrations and in dose-dependent manners without significant cytotoxicity. Moreover, these natural compounds reserved viral attachment, penetration, and spread to different degrees for each virus. Specifically, the tannins blocked all these steps of infection for HCMV, HCV, and MV.[26] Hydrolysable tannins possess remarkable HCV protease inhibitory activities. Casuarinin and chebulagic acid are non-protein and non-peptidomimetic inhibitors of HCV protease.[27]

Cardio-protective activities

Cardioprotective activities of tannin include anti-ischemic activity, vasorelaxant effect, myocardial infarction, and histamine release inhibitory effects. All these effects are exerted via stabilization of pericardial tissue,[29] inhibition of enzymatic degradation of elastin,[30] and reduction of the calcification of glutaraldehyde.[31] Among all species, hydrolysable tannins have anti-ischemic activity and endothelial-dependent effects possessed with the activation of the cyclooxygenase pathway, activation of endothelial nitric oxide synthase, scavenging of free radicals, and reactive oxygen species and with TNF-alpha inhibition etc.[32] It was also revealed that purified hydrolysable tannins caused NO- and cGMP mediated potent vasorelaxation in rat aortic rings. The phenolic hydroxyl groups of penta-*O*-galloyl-β-glucoside are essential for its vasorelaxant effects since its structure is without the hydroxyl groups. Several tannin-containing plants extracts markedly reduced the arterial blood pressure of hypertensive and normotensive rats in NO-dependent manner.[33] Similarly, tannic acid relaxed precontracted human coronary arteries and rat aortic rings in endothelium and in a NO-dependent manner.[34] The hydrolysable tannins possess an inhibitory effect on propranolol-induced negative inotropism, and the relative order of potency of the hydrolyzed tannins tested (praecoxin, 1-desgalloyl rugosin F) indicates that the galloyl group in the tannin structure is essential for the negative inotropic action. [35] Proanthocyanidins have long-lasting antihypertensive.[27,28] and vasorelaxant characteristics associated with endothelium-related factors.[36] It also has a significant effect on the heart providing protection against isoproterenol-induced myocardial infarction.[37]

Cytotoxic activity

Procyanidins possess cytotoxic activity.[30] which is due to the presence of a galloyl residue on the 3 positions of the C-ring. The potential anti-cancer properties evaluated for dimer procyanidins that contain galloyl groups, such as digalloyl dimer B1and B2 esters in a number of human cancer cell lines. Digalloyl dimer procyanidins exerted significantly higher cytotoxic effects than the structurally related complex tannins: EC, C, ECG, EGCG, (−)-catechin gallate (CG) and procyanidins B1 and B2. These results support the concept of incorporation of galloyl groups and the oligomerization of flavanols enhances the cytotoxic effects of typical monomer flavanols.[40] Catechins in tea leaves have been demonstrated in lab studies to prevent the growth of cancer cells. The antioxidant activity and direct binding capability to proteins results in the regulation of many cellular signaling pathways, are likely to be the cause of the anticancer effect, according to experimental investigations.[41] Another way of altering the cancer cells is inhibition of the release of tumor necrosis factor-α (TNF-α). This was observed for the hydrolysable tannins geraniin and corilagin in an assay for screening cancer-preventive agents suggesting that tannins of various structures could prevent cancer. The anticancer mechanism of action of most of the tannins include induction of apoptosis, inhibition of the inflammation signaling pathway, reducing the levels of MMP-2 and MMP-9 secreted to the extracellular medium, generation of an antioxidant environment, inhibition of DNA oxidative damage, and stimulation of the growth of beneficial colonic bacteria.[23]

Anti-diabetic Spectra of tannin

Tannins evoke potent anti-diabetic spectra. First, the ability to lower glucose levels by delaying intestinal glucose absorption and acting as an insulin-like agent on insulin-sensitive tissues. Secondly, tannins regulate the antioxidant environment of pancreatic β-cells and delay the onset of insulin-dependent diabetes mellitus. [4] Various tannins including vescalagin, acutissimin A/B, epiacutissimin A/B, grandinin/roburin E, hexagalloyl glucose and heptagalloyl etc. lower glucose level by inhibiting α-amylase and α-glucosidase activity. [34] Moreover, the anti-diabetic potential was significantly enhanced with the deficiency of protein molecules in the food contents and was also highly dependent on the order of accumulation of the enzyme and other substrate to tannins. Another study revealed the inhibition of human pancreatic α-amylase by tannin. The galloylated catechins have higher binding affinity with α- amylase than non- galloylated catechins.[35] It has been suggested

that the interaction between tannins e.g. galloylated quinic acid, and human α-amylase depends on the free hydroxyl groups on the tannins having hydrogen bond formation capability.[34]

Anti-inflammatory effects

The effect of different ellagitannins (geraniin, corilagin, furosin) extracts has been studied on animal model and it was found that these compounds abrogated bleomycin-induced lung fibrosis, reduced the number of apoptotic lung cells, and prevent lung epithelial cells from membrane breakdown.[39] There have also been studies on the possible wound healing capabilities of pentagalloylglucose (the major ingredient of Paeonia suffruticosa) and trigalloylglucose and gallic acid from Terminalia chebula. Strong anti-hyaluronidase and anti-elastase activity relating anti-inflammatory effects were also described for lythri herba.[38]

Hematopoietic stem cells preserving effects

Tannins in the Sanguisorba root can effectively preserve and treat cyclophosphamide–induced myelosuppression in mice.[41] The tannin fraction was administered by oral gavage at a dose of 20 mg/kg for 10 days after intraperitoneal administration of cyclophosphamide (200 mg/kg). These mechanistic actions might be related to protecting hematopoietic stem cells of bone marrow, stimulation of hematopoiesis restoration, and prevention of apoptosis of hematopoietic stem cells. The effect may result by promoting cells in the G2/M phase into the G1 phase, and it could promote the production of DNA photolyase and repair the damaged DNA after chemotherapy mutilation.[17,18]

Antiulcerant activity

Ulcers are a common widespread gastrointestinal disorder that includes infection of the gastrointestinal tract in the stomach or duodenum. It is basically an inflamed break in the skin or the mucous membrane lining the alimentary canal. Ulceration occurs when the usual equilibrium is disrupted by either increased acid aggression or decreased mucosal defensive activity.[39] It could be related to drug use on a frequent basis, a change in eating habits, stress, and so on. The genesis of peptic ulcers depends on the presence of acid and peptic activity in gastric juice plus an infection with *H. pylori*, a gram-negative bacterium. Tannins are used in medicine as an anti ulcerant due to their astringent properties which are due to the interaction of tannins with the tissue proteins and the formation of the tannin protein complex barrier. In gastric ulcers, this tannin-protein complex barrier protects the stomach by promoting greater resistance to chemical and mechanical injury or irritation. Moreover, in many studies, it was found that tannins have been shown to possess antioxidant activity, promote tissue repair, exhibit anti-*H. pylori* effects etc.[40]

CONCLUSIONS

This review study shows a wide range of studied activity of tannins and reflects in detail the gap regarding their pharmacological effect's spectra and mechanism of actions. Tannin and its products are an important class of secondary metabolites that have been found to exhibit many important pharmacological and physiological activities including antioxidant, anti-aging, anti-inflammatory, anticancer, mutagenic, antiatherosclerosis, cardioprotective, antiulcerogenic, hepatoprotective, antimicrobial, antiviral, vasodilator, and hypolipidemic activities. Medicinal preparations containing tannins are now considered as an indispensable component with external and internal effects in a variety of preparations. The external treatments are the treatment of skin inflammation and injuries and may prevent the inception of many chronic diseases. Tannin and its congeners inhibit lipid peroxidation and able to hunt cellular and molecular free radicals, especially in pro-oxidant states. Ellagitannin pedunculagin, possessing two hexahydroxy diphenyl groups and complex tannins including epigallocatechin gallate are proved to inhibit lipid peroxidation most potently. Several hydrolysable tannins eg pentagalloylglucose and geraniin were shown to inhibit xanthin– xanthine oxidase caused lipid peroxidation. Several dimeric tannins were found to have antibacterial action against methicillin-resistant *Staphylococcus aureus* (MRSA) and reduced the bacteria's resistance to oxacillin. They appear to exert these effects in a variety of methods, including inhibition of extracellular microbial enzymes, deprivation of the substrates necessary for microbial development, or direct action on microbial metabolism through inhibition of oxidative phosphorylation. Natural and synthetic tannins manifest activity against a large spectrum of viruses by the inhibition of the virus adsorption, inhibition of the virus penetration, inhibition of the virus adsorption/ penetration into the nucleus, and inhibition into the viral reverse transcription to the cell. Tannins have cardioprotective activities including anti-ischemic activity, vasorelaxant effect, myocardial infarction, and histamine release inhibitory effects etc. which are exerted via stabilization of pericardial tissue, inhibition of enzymatic degradation of elastin, and reduction of the calcification of glutaraldehyde. The anticancer mechanism of action of most of the tannins includes induction of apoptosis through, among other processes, activation of initiate or caspase-9, and effector caspase-3, inhibition of the inflammation signaling pathway, reduction of the levels of MMP-2 and MMP-9 secreted to the extracellular medium, generation of an antioxidant environment in the affected area, inhibition of DNA oxidative damage and stimulation of the growth of beneficial colonic bacteria. The first basis of the anti-diabetic spectra of tannin is its ability to lower glucose levels by delaying intestinal glucose absorption and acting as an insulin-like agent on insulin-sensitive tissues. Secondly, tannins regulate the antioxidant environment of pancreatic β-cells and delay the onset of insulin-dependent diabetes mellitus. These activities can be obtained by the inhibition of α-amylase and α-glucosidase activity. Geraniin, corilagin, furosin were found that these compounds abrogated bleomycin-

induced lung fibrosis, reduced the number of apoptotic lung cells, and prevented lung epithelial cells from membrane breakdown. Also, for pentagalloylglucose (main constituent of Paeonia suffruticosa) and for trigalloyl-glucose and gallic acid from *Terminalia chebula* reports have been published on potential wound healing properties. In the case of protection of hematopoietic stem cells of bone marrow, the mechanism might include, stimulation of hematopoiesis recovery, as well as prevention of the apoptosis of hematopoietic stem cells induced by cyclophosphamide. The effect may result by promoting cells in the G2/M phase into the G1 phase, and it could promote the production of DNA photolyase and repair the damaged DNA after chemotherapy damage.

Tannins are used in medicine as an anti-ulcerant for their astringent properties, which are due to interaction with the tissue proteins and the formation of the tannin protein complex barrier. In gastric ulcers, this tannin-protein complex barrier protects the stomach by promoting greater resistance to chemical and mechanical injury or irritation. Tannins are being used for a variety of reasons thanks to improvements in science and technology. The mechanism of action of tannin is based on the antioxidant activity due to their ability of electron donation and dependent upon the arrangement of functional groups. We would like to conclude that tannins are useful for plants, humans as well as animals. They can be employed for pharmaceutical purposes due to their presence in almost all vegetables and medicinal plants. Therefore, more attention is required in testing these compounds for the exploration of the expanded era of curative poses of human diseases.

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