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PYROGALLOL: A COMPETENT THERAPEUTIC AGENT OF THE FUTURE

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Abstract – Pyrogallol is a naturally occurring phenolic compound found to be present in *Emblica officinalis* (Amla or Indian Gosseberry), *Jatropha neopauciflora*, tea, coffee, avocado, apricot, etc. Pyrogallol falls in the category of tannins and is also known as 1,2,3-trihydroxy benzene and 1,2,3-benzenetriol. Intake of these kinds of compounds prevents oxidative damage to cell membrane lipid, protein, and nucleic acid due to the strong quenching property of free radicals and may protect against cardiovascular, immune/autoimmune diseases, and brain dysfunctions viz. Parkinson's, Alzheimer's, Huntington's diseases. Also, the puzzle of microbial resistance, which arises due to the uncontrollable use of antimicrobial drugs, can be solved by using these kinds of natural products in the treatment of various maladies. The popularity of these natural products to be used as novel antimicrobial agents is also because of no side effects shown by these compounds. Usually, phenolic compounds are known for their various biological properties such as antibacterial, antioxidant, antifungal, antiviral, antiseptic, anti-dermatitic, cardio protective, anti-mutagenic, pesticide, etc. The present study aims to focus on antibacterial, antifungal, anticancer, and antioxidant properties of pyrogallol as the prolific contributions have been made in the past by various researchers on these properties of pyrogallol. Pyrogallol can be used as a competent therapeutic agent in the future. However, the mechanism of antimicrobial action of pyrogallol is still unknown and needed to be studied. This review article is an endeavor to harmonize the knowledge about the utility of pyrogallol in the extirpation of various ailments.

INTRODUCTION

After the discovery of antibiotics and other antimicrobial agents, it was believed by the healthcare community that the solution to the problem of infectious diseases has been discovered. However, nowadays many microbes are becoming resistant to antimicrobial agents, the solution to the problem of infectious diseases is still not clear (Reygaert *et al*., 2018). Worldwide microbial infections are known to be responsible for millions of death every year. The use of natural products as novel antimicrobial agent is now become the new and popular strategy against microbial resistance. These natural products can be used alone or in combination with failing antibiotics, which can restore the desirable antibacterial activity of these antibiotics. One such natural product is pyrogallol, which is a polyphenolic compound known to have various biological properties such as antibacterial (Cynthia *et al*., 2018), antioxidant (Biskup *et al*., 2013), antifungal (Hirasawa and Takada, 2004), antiviral, antiseptic, antidermatitic, cardioprotective, antimutagenic and pesticide, etc (Defoirdt *et al*., 2013; Singh and Kumar, 2013; Balasubramanian *et al*., 2014). Pyrogallol is also known as 1,2,3-trihydroxybenzene and 1,2,3-benzenetriol. Pyrogallol is a naturally occurring phenolic compound found to be present in various plants such as *Emblica officinalis* (Amla or Indian Gosseberry) (Balasubramanian *et al*., 2014; Bhandari and Kamdood, 2012); Terminaliachebula (Black Myrobalan and Harad) (SreeGayathri *et al*., 2015); *Jatropha neopauciflora* (Hernández *et al*., 2017); *Jatropha curcas* (Namuli *et al*., 2011), *Entada abyssinica* tree (Teke *et al*., 2011); tea and coffee (Mendes *et al*., 2015); *Cassia siamea* (Kassod tree) (Vani *et al*., 2019); *Labisia pumila* (Othman *et al*., 2016); *Rumex*

obtusifolius (Nazari *et al*., 2017); avocado and apricot (Sarikaya, 2014), etc. Also, some lactic acid bacteria such as *Lactobacillus brevis*, *Lactobacillus fermentum*, and *Lactobacillus plantarum* are known to metabolize phenolic acids by the process of decarboxylation and reduction and can form pyrogallol as one of the end product (Sa´nchez-Maldonado *et al*., 2011). The toxicity of pyrogallol against microorganisms is believed due to the presence of three hydroxyl groups. The number and location of hydroxyl groups in the phenolic compounds are the key factors in their toxicity to microorganisms. As the number of the hydroxyl groups increases, so does the toxicity (Colak *et al*., 2010). Pyrogallol falls in the category of tannins and dietary intake of such type of compounds causes the reduction of oxidative damage to cell membrane lipid, protein, and nucleic acid due to strong quenching property of free radicals. Hence, these compounds can protect against cardiovascular, immune/autoimmune diseases, and brain dysfunctions viz. Parkinson's, Alzheimer's, Huntington's diseases (Tadic *et al*., 2017). Some researches have been carried out on the biological properties of pyrogallol, and this compound has the caliber to solve various issues related to the healthcare community. Hence, in the present study, the above-mentioned properties of pyrogallol, discussed and proved experimentally in various studies are included and reviewed.

Antibacterial activities of Pyrogallol

As discussed above, there is an urgent need for novel antibacterial agent. Pyrogallol can perform the function of the novel antibacterial agent as there are many studies that proved the antibacterial property of pyrogallol against various bacterial species. Pyrogallol at 5mM concentration showed the inhibitory action against *Pseudomonas putida*, *Pseudomonas pyocyanea*, and *Corynebacterium xerosis*. A broad-spectrum anti-bacterial property of pyrogallol was observed by Kocacaliskan *et al*., 2006. In another study pyrogallol showed the potent antibacterial action against 23 bacterial isolates including *B. cereus*, *B. subtilis*, *L. monocytogenes*, *S. aureus*, *C. michiganensis*, *Aeromonas hydrophila, Vibrio parahaemolyticus, Vibrio vulnificus, Citrobacter freundii, Escherichia coli, Klebsiella pneumoniae, Salmonella* anatum, *Salmonella arizonae, Shigella flexneri, Shigella sonnei, Yersinia enterocolitica, Erwinia carotovora, Pseudomonas aeruginosa*, *Pseudomonas cichorii, Pseudomonas marginalis, Pseudomonas viridiflava, Agrobacterium tumefaciens* and *Xanthomonas campestris*. Pyrogallol also showed the broad-spectrum antibacterial activity against gram-positive as well as gram-negative bacterial isolates (Taguri *et al*., 2006). Similarly, in another study pyrogallol showed antibacterial activity against many bacterial isolates which was evaluated by determining MIC. The activity of pyrogallol was observed against *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Shigella flexneri*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Escherichia coli* (Teke *et al*., 2011). Pathogenic *Vibrio parahaemolyticus* isolates, isolated from stomach and hepatopancreas of white leg shrimps were also found to be inhibited by the action of pyrogallol at the concentration between 32-64 µg/ml (Tinh *et al*., 2016). On the other hand, a dose-dependent inhibition of *V. vulnificus* cells was observed by pyrogallol which further showed complete inhibition at 37.6 µg/ml concentration (Lim *et al*., 2016). In another study, antibacterial activity of pyrogallol and its synthetic dimer against *Staphylococcus aureus* and *Escherichia coli* was evaluated. It was observed that the pyrogallol dimer showed the inhibitory action against both the bacterial isolates but pyrogallol showed the action only against *S. aureus* and no inhibitory action of pyrogallol was observed against *E. coli*. It was concluded in the study that dimerization of pyrogallol enhanced the antibacterial activity of pyrogallol against gram-positive as well as gram-negative bacterial isolates (Cynthia *et al*., 2018).

In some of the studies, pyrogallol was observed as the active and major component of plants and was believed as the main reason behind the antibacterial activity of the plant extracts. In a study pyrogallol (291.40 mg/g) was observed as the main component in ethyl acetate extract of aerial parts of *Rumex japonicas*. Antibacterial activity of pyrogallol containing ethyl acetate extract was observed against *Bacillus subtilis*, *Bacillus cereus*, and *Escherichia coli* (Elzaawely *et al*., 2005). In another study, different parts (root, stem, and leaf) of *Labisa pumila* Benth Alata variety which was observed to contain pyrogallol was found to show antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Bacillus cereus*, *Micrococcus luteus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus aerogenes*, and *Klebsiella pneumoniae*. While the other two varieties that do not have pyrogallol as the component did not show any antibacterial action against these bacterial isolates (Karimi *et al*., 2011). Pyrogallol extracted from *Terminalia chebula* ethyl

acetate fruit essential oil was found to show inhibitory action against *Escherichia coli*, *Proteus mirabilis*, *Raoultella planticola*, *Enterobacter aerogens*, *Bacillus subtilis*, and *Staphylococcus aureus* (Singh and Kumar, 2013). A significant antibacterial activity of pyrogallol was also observed against *Enterococcus faecalis* and *Escherichia coli* isolated from clinical urine samples (Sahare and Moon, 2016 a; Sahare and Moon, 2016 b).

During urinary tract infection, an antimicrobial protein known as siderocalin (SCN) is released from host cells which bind to ferric catechol complexes and sequester iron (a growth-limiting nutrient for most bacterial pathogen). Pyrogallol was also observed to play the role of SCN ligand and in the enhancement of siderocalin activity for the inhibition of bacterial pathogen (Shields-Cutler *et al*., 2016). In another study, synergistic activity of pyrogallol was shown in combination with norfloxacin and gentamicin against *S. aureus*. It was observed that in association with norfloxacin, pyrogallol reduces the MIC from 156.3 mg/ml to 78.13 mg/ml and in association with gentamicin it reduced the MIC from 49.21 mg/ml to 2.44 mg/ml (Lima *et al*., 2016). A hydrogel (GelTHB-Fe) containing pyrogallol moieties was prepared for the investigation of wound healing properties. It was observed that the presence of pyrogallol moieties impart an antibacterial activity to the GelTHB-Fe hydrogel, which is shown to reduce infection and promote wound healing in a diabetic rat model (Han *et al*., 2020).

Antifungal activities of Pyrogallol

Pyrogallol was also observed to possess antifungal properties against some fungal species as investigated in some studies. Fruits of *Terminalia chebula* were observed to have pyrogallol as the main component and also believed to be responsible for the antimicrobial property of *Terminalia chebula* fruits. Pyrogallol extracted from the plant was found to inhibit *Aspergillus flavus* and *Candida albicans* (Singh and Kumar, 2013). Similarly in another study pyrogallol was found as the main component of *Rumex obtusifolius* seed extract, which showed a very potent antifungal property against *Candida albicans*. The reason behind the significant antifungal property of *Rumex obtusifolius* seed extract was observed the presence of phenolic compounds in the seed extract especially pyrogallol (Nazari *et al*., 2017).

Anti-cancer activities of Pyrogallol

The attention of scientist and researchers is mainly focusing on the natural compounds to treat cancer because of their less toxic side effects in comparison to the current treatments such as chemotherapy (Greenwell and Rehman, 2015). Pyrogallol is derived from natural sources and possesses anti-cancer property. In a study, pyrogallol was investigated for its tumor-promoting activity in mouse skin for 440 days, and pyrogallol was observed to have no tumor-promoting activity. However, pyrogallol was mentioned as a carcinogen in the same study, as suggested by the authors that there is no correlation between carcinogenic property and tumor-promoting property (Duuren and Goldschmidt, 1976). Pyrogallol showed antiproliferative effects on human tumor cell lines such as K562, Jurkat, Rajij, and HEL and inhibit the growth of these tumor cell lines. The authors proposed this compound to be studied more in the future for its possible anti- tumor activity *in vivo* (Khan *et al*., 2002). In another study pyrogallol at IC_{50} of ~50 μM showed the dose-dependent inhibition of SNU-484 gastric cancer cells by inducing apoptosis within 72hrs (Park *et al*., 2008). Not only pyrogallol but also polyphenols having pyrogallol structure also showed the cytotoxic activity against HEK293T and K562 cell lines by causing DNA laddering, in a non-oxidative mechanism. Hence, it was observed that the pyrogallol moiety is important for acting on targets in a non-oxidative mechanism (Mitsuhashi *et al*., 2008). Some pyrogallol-based arylspiroborates were synthesized and then evaluated for their anti-cancer property. These arylspiroborates salts showed a significant anti-cancer property against renal cell carcinoma cell lines without affecting the healthy cells (Cormier *et al*., 2015).

Anti-oxidant activities of Pyrogallol

Natural antioxidants are under research due to their capability to prevent oxidative stress as well as for their various biological properties (Cardoso, 2019). Pyrogallol is a compound that possess both antioxidant as well as prooxidant properties, i.e. the ability to generate reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2) (Baruah *et al*., 2015). The antioxidant property of seed extract of *Rumex obtusifolius* was observed in a study and it was concluded that the antioxidant property was mainly due to the presence of pyrogallol in the seed

extract (Nazari *et al*., 2017). Similarly, the extract of aerial parts of *Rumex japonicus* also showed the antioxidant property which was again believed because of the presence of pyrogallol in the extract (Elzaawely *et al*., 2005). In another study various *in vitro* assays such as ferric thiocyanate method, DPPH scavenging, ABTS scavenging, DMPD scavenging, Fe_{2+} chelating, O_2 scavenging and H_2O_2 scavenging activities, Fe^{3+}– Fe^{2+} and Cu^{2+} – Cu^{+} reducing power assays were performed for the evaluation of antioxidant property of pyrogallol. It was observed that pyrogallol is a more powerful antioxidant in comparison to the standard antioxidant compounds such as BHA, BHT, α-tocopherol as a natural antioxidant, and trolox (Sarikaya, 2014). It was also explained in a study that pyrogallol is involved in superoxide anion (O_2^-) generation which is also known as reactive oxygen species (ROS). ROS species are known to play the role in the regulation of many important cellular events, including transcription factor activation, gene expression, differentiation, and cell proliferation in normal cells. On the other hand, it was also observed that pyrogallol induces O_2^- mediated cell death of cancer cells such as human lymphoma cells, human glioma cells, and Calu-6 lung cancer cells (Han *et al*., 2010). Pyrogallol moiety was found essential for the good antioxidant property (Venkateswarlu *et al*., 2005). The presence of the hydroxyl groups in the ortho position of the B ring in pyrogallol plays the main role in the contribution to the antioxidant property of pyrogallol (Mendes *et al*., 2015).

Concluding Remarks and Future Perspectives

As discussed above, pyrogallol is found to possess antibacterial and antifungal properties against various bacteria and fungi respectively. Being obtained from natural sources, pyrogallol can be considered safe to be used for the treatment of several microbial diseases. The anticancer property of pyrogallol was also evaluated by several *in vitro* and *in vivo* studies and pyrogallol has well-established chemopreventive activity against many types of cancer. In addition to that, pyrogallol also showed antioxidant property which was confirmed with the help of various biochemical tests. However, more research is still required for the investigation of the mechanism of antimicrobial action of pyrogallol. Based on above-mentioned properties, the use of pyrogallol for therapeutic purposes should be considered. As in the future, pyrogallol can work as a promising drug in fighting many ailments.

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