

## ***Emblica officinalis* (Amla) with a Particular Focus on Its Antimicrobial Potentials: A Review**

Sandip Kumar Khurana<sup>1</sup> , Ruchi Tiwari<sup>2</sup> , Khan Sharun<sup>3</sup> , Mohd. Iqbal Yattoo<sup>4</sup> , Mudasir Bashir Gugjoo<sup>5</sup>  and Kuldeep Dhama<sup>6\*</sup> 

<sup>1</sup>ICAR-Central Institute for Research on Buffaloes, Hisar - 125 001, Haryana, India. <sup>2</sup>Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, Deen Dayal Upadhyay Pashu Chikitsa Vigyan Vishwavidyalay Evum Go-Anusandhan Sansthan (DUVASU), Mathura, India – 281 001, India. <sup>3</sup>Division of Surgery, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly - 243 122, Uttar Pradesh, India. <sup>4</sup>Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar - 190 025 Srinagar, Jammu and Kashmir, India. <sup>5</sup>Division of Veterinary Clinical Complex, Faculty of Veterinary Sciences & Animal Husbandry, Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar - 190 025 Srinagar, Jammu and Kashmir, India - 190 006. <sup>6</sup>Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly - 243 122, Uttar Pradesh, India.

### **Abstract**

*Emblica officinalis* Gaertn. or *Phyllanthus emblica* Linn., popularly called as Indian gooseberry or Amla, is among main herbal plant in Indian traditional medicine. Different parts of *E. officinalis* are beneficial for curing various ailments but the fruits especially show tremendous pharmacological and medicinal applications. Phytochemical analysis revealed important bioactive chemical compounds such as tannins, alkaloids, polyphenols, gallic acid, ellagic acid, emblicanin A and B, phyllembin, quercetin, ascorbic acids, vitamins and minerals. Different extracts of amla possess potent antimicrobial activities to counter different bacterial pathogens. Amla phytochemicals also possess antioxidant, anti-inflammatory, hepatoprotective, cardioprotective, immunomodulatory, hypolipidemic, memory enhancing, anticancer, antidiabetic, antidepressant, anti-ulcerogenic, insecticidal, larvicidal, and wound healing activities. All of these well-established activities can have broad applications in managing most of the diseases affecting human and animal patients. It can either replace the conventional therapeutic agents due to its superior efficacy and lack of side effects or can act an adjunct therapeutic agent thereby enhancing the total efficacy of conventional agents. The biogenic synthesis of nanoparticles from *E. officinalis* is getting popularity due to the low cost factor along with the enhanced antimicrobial activity of the nanoparticles produced. The current review emphasizes on the phytochemical constituents, mechanisms behind the antimicrobial activity and also briefly summarizes other medicinal and therapeutic usefulness of the *E. officinalis*.

**Keywords:** *Emblica officinalis*, Amla, Antimicrobial effects, Phytochemicals, Pharmacological activity, Therapeutic usefulness, Health.

\*Correspondence: [kdhama@rediffmail.com](mailto:kdhama@rediffmail.com)

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## INTRODUCTION

Medicines of natural origin like herbs and plant metabolites / extracts are being used since long as beneficial remedies for managing and curing several diseases and disorders for protecting health of humans and animals<sup>1-6</sup>. Plants and herbs are a rich source of developing effective and alternative / complementary therapeutic drugs and medicines. Over the years several drugs have been developed that have made significant contributions to human health and wellbeing<sup>6,7</sup>. WHO has also approved the usage of herbal medicines for curing various diseases, from malaria to cancer<sup>8,9</sup>. *Phyllanthus emblica* syn. or *Emblica officinalis* (EO) (family *Euphorbiaceae*), also called 'Indian gooseberry' and 'Amla', is placed in category of most significant medicinal plants in traditional system of Indian medicine (Ayurveda)<sup>10-17</sup>. EO is a native herb of Indian tropical and subtropical regions, and is also found in Sri Lanka, Uzbekistan, South East Asia, and China nowadays<sup>18</sup>. EO possess vast beneficial health applications in traditional system such as liver tonic, diuretic, laxative, improving digestion, anti-pyretic, hair tonic, anti-ulcer, curing common cold and fever<sup>13,19-23</sup>. It also play role in enhancing memory, lowering cholesterol levels, neutralizing snake venom, curing infectious diseases and usage as a potent immunomodulator<sup>24</sup>.

The EO fruit contains high vitamin C and other bioactive compounds such as polyphenols, ellagic acid, chebulinic acid, gallic acid, chebulagic acid, aepigenin, quercetin, corilagin, and leutolin<sup>11,15,16</sup>. Sugar-substituted phenolics (flavone, phenolic, flavonol glycosides)<sup>15</sup>, tannins (emblicanin A and B, phyllaemblicin B, punigluconoin) are present in fruit pulp<sup>16,25,26</sup>. Amla extracts have been extensively investigated for different biological activities<sup>15</sup>. These phytochemicals contribute to the antibacterial, antifungal, antiviral and other pharmacological activities<sup>27,28</sup>. Recent *in vitro* studies have revealed antiinflammatory<sup>29</sup>, antioxidant<sup>30,31</sup>, cytoprotective<sup>32</sup>, antiaging<sup>33</sup>, nephrotoxicity modulation<sup>34</sup>, antidiabetic<sup>35</sup> and hepatoprotective<sup>36</sup> properties of amla. Some of the other applications includes anti-diarrheal, immunomodulator, gastroprotective, cardioprotective, analgesic, antipyretic, wound healing, antitussive, anti HIV-reverse transcriptase, insecticidal, larvicidal,

antidepressant, neuroprotective, and radio-protective activity<sup>15,16,37</sup>. All of these actions are utilized for therapeutic purposes of conditions like tumors, cardio-respiratory disorders, diabetes, atherosclerosis, thrombotic events, osteoporosis, and neuropathy<sup>15</sup>. Antimicrobial resistance, a rising public health concern, need to be tackled with finding out alternative, complementary and novel therapeutic regimens<sup>38,39</sup>. Medicinal herbs and plant extracts contain various bioactive constituents / phytochemicals having potent antimicrobial properties, while showing no toxic or adverse side effects<sup>3,19,40</sup>.

The present review highlights the antimicrobial potential, phytoconstituents and modes of action of *Emblica officinalis* and its extracts in humans and animals. Other pharmacological activities and beneficial health applications have also been discussed in brief.

## METHODS

### Antimicrobial activities

Several studies have been conducted to assess antimicrobial potential of different extracts of plants in the past decades. Most of the plant extracts evaluated were found to display significant antimicrobial action mostly due to several active constituents present in them<sup>3,6,7</sup>. *Emblica officinalis* has shown effective antimicrobial properties and usefulness for the designing effectual medicines<sup>13,16,21,22,24,37,41,42</sup>. The EO extracts posses antimicrobial properties like antifungal, antiviral and antibacterial activities<sup>17,28,43-46</sup>, and thus this plant is being explored for developing novel and alternative antibacterial and complementary treatment options in biomedical science owing to its potent medicinal values<sup>5,10,11,15,17,37,47,48-50</sup>.

### Antibacterial activity

The antibacterial action of EO is higher for Gram-positive bacteria, while its effectiveness is limited for countering fungi<sup>51-53</sup>. The extracts of EO exhibited high zone of inhibition (ZOI) when tested for *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Bacillus cereus*, *Vibrio cholerae* and *Candida albicans*<sup>54</sup>. Antimicrobial effectiveness for Gram-positive, Gram-negative bacteria along with fungal agents reflects usage of fruit of *P. emblica* as a remedy for different microbial diseases<sup>50</sup>.

The extracts of triphala and amla, obtained with aqueous and ethanolic solvents, showed antibacterial action for *Pseudomonas aeruginosa*, *K. pneumoniae*, *Shigella sonnei*, *Shigella flexneri*, *S. aureus*, *V. cholerae*, *Salmonella paratyphi-B*, *E. coli*, *Enterococcus faecalis* and *Salmonella typhi*<sup>55</sup>. Gallic and tannic acid, main phytoconstituents of EO, possess strong antimicrobial potential<sup>19</sup>. *In vitro* assessment of EO fruit and leaf showed 100 percent antibacterial, antiprotozoal and antifungal activities. In another study, EO demonstrated effective antibacterial action for *E. coli*, *K. pneumoniae*, *K. ozaenae*, *P. mirabilis*, *P. aeruginosa*, *S. typhi*, *S. paratyphi A & B*, *S. marcescens*, while was not effective against few Gram-negative urinary pathogens<sup>56</sup>. A long-term feeding (30 days) study in mice for finding protective effects of *P. emblica* against *K. pneumoniae*-induced pneumonia revealed that *P. emblica* supplementation reduced colonization of bacteria in the lungs<sup>57</sup>.

*P. emblica* and its extract possess antimicrobial and cytotoxic activities. The chloroform extract of *P. emblica* fruit revealed powerful inhibitory action for *B. subtilis* and moderate inhibition for *S. typhi*, *Bacillus cereus*, *P. aeruginosa*, *Shigella boydii*, *Shigella dysenteriae*, *S. aureus*, *Sternbergia lutea*, *E. coli*, *S. paratyphi*, *Vibrio parahaemolyticus* and *Vibrio mimicus*<sup>52</sup>. *In vitro* antibacterial action of EO fruit (ethanolic extracts) has been also reported against *V. cholerae*, *S. aureus* and *P. aeruginosa* isolates<sup>58</sup>. Aqueous extract of EO showed antibacterial effectiveness to inhibit *E. coli*, *B. subtilis* and *S. aureus* isolates<sup>59</sup>. Methanolic extracts of *P. emblica* dried leaves showed antibacterial activity for two pathogenic bacteria, *B. subtilis* and *S. aureus*<sup>60</sup>. EO aqueous fruit extracts revealed potent antibacterial effects for five human bacterial pathogen stock cultures, namely *Bacillus sp.*, *Lactobacillus sp.*, *Pseudomonas sp.*, *Proteus sp.*, *Streptococcus* species<sup>61</sup>. Different extracts of EO fruit tested against pathogens *viz.*, *E. coli*, *S. marcescens*, *P. aeruginosa* and *B. cereus*, showed highest antibacterial action for *E. coli* by methanol extract followed by aqueous extract<sup>62</sup>.

The ethanolic extracts of henna, neem and amla revealed antimicrobial action against *E. coli*, while tulsi extract showed high antimicrobial action for *Klebsiella*<sup>63</sup>. Extracts of six medicinal

plants revealed variable antimicrobial potential for oral pathogen *S. mutans*; crude extract of garlic showed high effectiveness (maximum zone of inhibition, ZOI) as compared to aqueous extract of amla and organic solvent of ginger<sup>24</sup>. The crude extracts of EO fruit in different solvents like hexane, chloroform and methanol revealed antibacterial activity against *E. coli*, *K. pneumoniae*, *P. vulgaris*, *M. luteus*, *B. subtilis*, *E. faecalis* and *S. faecalis*. The hexane extract showed less antibacterial action as compared to the chloroform and methanol extracts<sup>64</sup>.

Antimicrobial activity studied for different extracts of *P. emblica* revealed that the MIC exhibited by methanolic extract of amla against the tested organisms ranged between 0.261-0.342, this extract was found to have more antimicrobial property than chloroform and diethyl ether extracts<sup>65</sup>. Among *P. emblica* fruit extracts, highest ZOI for bacterial growth got obtained at 100 mg/ml at pH 8.0, followed by *K. pneumoniae* ATCC 31488 and *S. aureus* in ethanol solution extract<sup>66</sup>. Methanol extract of amla fruit has been found to be more potent for *S. aureus*, *E. coli* and *K. pneumoniae* as compared with methanolic leaf extract<sup>67</sup>. The crude extract of amla leaves showed highest inhibition for *E. coli* while lowest for *S. typhi*<sup>68</sup>. Acetone fruit extract was found to have maximal antibacterial action for *E. coli*, while methanol as well as aqueous extracts showed maximum activity for *S. aureus* and *K. pneumoniae*, respectively<sup>19</sup>. Antimicrobial potential of EO methanolic seed extract has been reported against *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. aureus* and *Enterococcus* clinical isolates, with maximum ZOI observed for *S. aureus* while to be lowest for *P. aeruginosa*<sup>42</sup>. Aqueous, ethanol and acetone extracts of EO fruits have been reported to have noteworthy antibacterial action for *S. aureus* as compared to *E. coli*<sup>69</sup>. The petroleum ether leaf extract of EO exhibited potent antibacterial and antifungal properties for all tested pathogenic strains in human except for *E. faecalis*<sup>70</sup>.

*P. emblica* extract was observed to possess high antimicrobial effects for Gram-positive, Gram-negative as well as resistant bacteria; the highest being observed against *B. subtilis* as indicated by the high ZOI (25 mm), while lowest against *S. paratyphi*, *Pseudomonas spp.*, *S. typhi* as evident from the lower ZOI (8 mm)<sup>71</sup>. The

aqueous extract gave the highest ZOI against *B. subtilis* followed by *E. coli*. The 5% aqueous extract of Amla has been reported to exhibit the highest ZOI, indicating potent antibacterial activity<sup>46</sup>. The potent antibacterial activity of EO against several microorganisms can be credited to tannins present in its fruits. Emblicanin A and B are the two major tannins that give antimicrobial property to the fruit extract of *E. officinalis*<sup>64</sup>. The tannins produce antimicrobial action due to the capability to inhibit microbial adhesions, inactivate enzymes, and cells envelop transport proteins<sup>72</sup>. Another compound Phyllembin present in *E. officinalis* has significant antibacterial activity against several mastitis causing agents like *S. pyogenes*, *S. aureus* and *K. pneumoniae*<sup>67,73</sup>.

Aqueous and methanolic extracts of EO fruits have well established antibacterial activity that varied among the Gram positive and negative groups of bacteria<sup>74</sup>. *E. officinalis* is more effective against Gram-positive than Gram-negative bacteria, which may be due to differences in structure and composition of the cell wall<sup>62</sup>. A similar spectrum of activity was exhibited by phytofabricated selenium nanoparticles (PF-SeNPs) produced from EO fruit aqueous extract. The reduced antibacterial potential of PF-SeNPs for Gram negative bacteria may be due to strong electrostatic repulsion existing between PF-SeNPs and the Gram negative bacterial lipopolysaccharide which prevents their interaction<sup>75</sup>. Antimicrobial property of EO fruit extracts assessed for pathogens like *E. coli*, *S. aureus* and *S. typhi*<sup>28</sup> revealed maximum activity for *S. aureus* by methanolic extract. The result suggests that the fruit extract produces maximum inhibition against Gram-positive rather than Gram-negative bacteria, again confirming superior antibacterial effectiveness of EO for Gram-positive bacteria. Screening the juices of gooseberry and wild apple for antibacterial and antifungal potentials revealed significant levels of antibacterial action for drug-resistant microbes (methicillin-resistant *S. aureus*, vancomycin-resistant Enterococci,  $\beta$ -lactamases producing Gram-negative bacteria)<sup>76</sup>. The antimicrobial evaluation of Indian gooseberry and galangal (*Alpinia galanga*) extracts for *S. aureus* revealed MIC values of 13.97 and 0.78 mg/ml, and minimum biocidal concentration (MBC) of 13.97 and 2.34

mg/ml, respectively<sup>77</sup>. The antimicrobial activity of the leaves and fruit extracts of *P. emblica* has also been proven for *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli*<sup>78</sup>. Short term use of *P. emblica* fruit gum (sugar free chewing gum prepared by addition of 10% *P. emblica* fruit extract) was found effective in altering oral microbiome and produced a noteworthy decrease of the total bacterial count and decrease in salivary levels of *S. mutans* and *Porphyromonas gingivalis*<sup>79</sup>. The inhibition of growth and activity of oral microbes will play a crucial role in prevention of dental caries.

The ethyl acetate EO fruit extract showed powerful inhibitory action for bacterial triggers of autoimmune inflammatory disorder<sup>27</sup>. It acted as an effective inhibitor of *P. aeruginosa* and produced moderate to powerful inhibition of *P. mirabilis*, *K. pneumoniae* and *Acinetobacter baylyi*. Methanolic and aqueous extracts showed moderate to low inhibition of all tested bacteria. In another study, different Gram negative bacteria (*P. aeruginosa*, *E. coli*, *V. cholera*, *S. typhi*, *S. dysenteriae*, *P. mirabilis*, and *Providencia alcalifaciens*) and Gram positive bacteria (*S. aureus*, *B. subtilis*, *B. megaterium*, *B. pumilus*, *B. cereus*, *S. pyogenes*, *B. polymyxa*) showed susceptibility to the aqueous and methanolic extracts of EO fruits at 500–1000 $\mu$ g/mL<sup>74</sup>.

Methanolic extract of EO showed good antimicrobial action against *E. coli*, *Salmonella* and *S. aureus*<sup>48</sup>. Owing to potent antibacterial effectiveness of EO essential oil countering *S. aureus*, it can be used for the treatment of diseases involving *S. aureus*<sup>80</sup>. Antimicrobial assessment of crude powder, aqueous and methanolic extracts of fruit and leaf of EO for *S. aureus*, *K. pneumoniae*, and *S. pyogenes* revealed that methanolic extract caused major changes in biochemical features of these pathogens<sup>67</sup>. The antibacterial activity study of amla phenolic extract revealed highest inhibition zone for *S. aureus* followed by *Bacillus* spp., *E. coli* and *Proteus* spp<sup>81</sup>. A comparative study evaluated antimicrobial effectiveness of different agents against the bacteria *E. faecalis*. The zone of microbial growth inhibition of *E. officinalis* was higher than 2.5% sodium hypochlorite indicating superior antibacterial activity of EO extract<sup>72</sup>. The therapeutic effectiveness of EO fruit extract and procaine penicillin was studied for treating subclinical mastitis in dairy buffaloes<sup>73</sup>. In this

study, one group received intramammary infusion procaine penicillin at a dose of 2,000,000 I.U and the other group received intramammary infusion of *P. emblica* fruit extract at 1500 mg (5 ml) for 5 days. Both the groups showed slight difference in the cure rate on 7<sup>th</sup> day, but the percentage of cured animals was moderately higher in the procaine penicillin treated group on day 14, indicating almost similar efficacy of both treatment protocols in the treatment of subclinical mastitis. Hence intramammary therapy using *P. emblica* fruit extract can be considered as an effective replacement or as an adjunct for antibiotics in buffaloes for management of subclinical mastitis. The organic extracts of EO leaves revealed low to moderate *in-vitro* antibacterial potential along with bacteriostatic activity countering several antibiotic resistant isolates of the opportunistic fish pathogen *E. faecalis*.<sup>82</sup>

#### Antifungal activity

The *P. emblica* extract analyzed for *in vitro* potential against *Fusarium solani*, a fungal agent causing dry potato tuber rot revealed inhibition of mycelial growth at a 100% concentration<sup>83</sup>. The aqueous extract of EO reported significant antifungal activity against eight species of *Aspergillus* fungi (*Aspergillus candidus*, *A. columnaris*, *A. flavipes*, *A. flavus*, *A. fumigatus*, *A. niger*, *A. ochraceus*, and *A. tamari*)<sup>84</sup>. In this study, different solvents employed for the extraction process included Petroleum ether, Chloroform, Methanol, Benzene, and Ethanol. Among different solvents used, methanol extract of EO exhibited superior antifungal activity compared to the other solvents<sup>84</sup>. Ethanol and acetone extracts of fruit had moderate inhibition towards *F. equiseti* and *C. albicans*, wherein Grisofulvin employed as standard antifungal agent<sup>44</sup>. Plant methanolic extract of EO was not having antifungal activity for phytopathogenic fungus *A. niger* F2723<sup>85</sup>. The aqueous extracts of EO revealed a diverse degree of antimicrobial action for the pathogenic microbes viz., *S. aureus*, *E. coli* and *Candida* species<sup>86</sup>. The ethanolic extract of EO has been observed to interfere *in vitro* with adhesion process of *C. albicans* to the human buccal epithelial cells (BECs) and denture acrylic surfaces<sup>87</sup>. *E. officinalis* extracted using ethanol solvent revealed moderate inhibitory action for *S. aureus*, *S. typhi*, *B. subtilis*, *S. dysenteriae* and *B. megaterium* whereas acetone

extracts had moderate action for *V. cholerae*, *S. aureus*, *B. subtilis* and *S. dysenteriae* compared with the standard antibiotic (Amoxicillin)<sup>44</sup>. On antifungal screening, both the extracts possessed moderate activity for *F. equiseti* and *C. albicans*. In this case, griseofulvin was used as the standard antifungal agent<sup>44</sup>. The ethanol, acetone and water (distilled) extracts of EO when assessed for *S. mutans*, *E. faecalis* and *C. albicans* showed minimum inhibitory concentration (MIC) at 0.09% for ethanolic and acetonic extracts for *C. albicans*, and at 1.56% for water extract. MIC of ethanolic extract for *E. faecalis* was at 3.12%, acetonic extract at 0.39% and water extract at 12.5%<sup>88</sup>. Ethyl acetate extract of leaf and bark exhibited maximum potency against *Rhizomucor* species, whereas methanolic extract showed lowest inhibition against this fungus<sup>89</sup>.

Methanolic extract of amla revealed significant inhibitory action for *S. aureus*, *E. coli* and *Candida* species as compared with ethyl acetate and aqueous extract<sup>86</sup>. *In vitro* study with fruit extracts of *Sapindus mukorossi* and EO against *S. mutans*, *S. aureus*, *Lactobacillus acidophilus*, *C. albicans* and *Saccharomyces cerevisiae* depicted fruits of *S. mukorossi* and EO to have potent antifungal and antibacterial effects, respectively<sup>90</sup>. *Triphala* inhibited *Aspergillus* species *in vitro* by up to 37.96%. Aqueous extracts of fresh fruits have proven potent antimicrobial effects than dry fruits<sup>91</sup>. The antimicrobial potency of the extract from endophytic fungi of EO when tested against *E. coli* MTCC730, *Enterococcus faecalis* MTCC2729, *Salmonella enteric ser. Paratyphi* MTCC735 and *Streptococcus pyogenes* MTCC1925, and *C. albicans* MTCC183 revealed inhibition of the growth of all organisms except *E. coli*<sup>92</sup>. This might also contribute to the antimicrobial action of different kind of extracts obtained from EO plant. In another study, it was found that seven pathogenic strains of fungi (*A. niger*, *Neurospora crassa*, *P. chrysogenum*, *T. viride*, *A. brasiliensis*, *C. albicans* and *Cladosporium oxysporum*) were found to be susceptible to aqueous extract of EO fruit at a high concentration of 500µg/mL<sup>74</sup>.

Hexane and methanol extracts of EO when assessed for effectiveness against *Fusarium oxysporum* and *Rhizoctonia solan*, revealed that fractions collected from the methanol extract proved more effective against both test

pathogens<sup>93</sup>. Fraction 112 and 106 possessing 1,2-dihydroxyethyl-3,4-dihydroxyfuran-2(5H)-one and 2,3,7,8-tetrahydroxy-chromeno [5,4,3-cde] chromene - 5,10-dione proved most inhibitory to *F. oxysporum* and *R. solani*, respectively. It was also observed that whole fraction exhibited more inhibition than pure constituent(s) isolated from the respective fraction(s)<sup>93</sup>. The antifungal effectiveness of extracts of EO fruits, *Aloe vera* and *Vitex negundo* leaves were screened against *A. niger*, *A. flavus*, *A. oryzae*, *P. chrysogenum* and *T. viride*. All of the plants revealed maximum potential against *T. viride* while *P. chrysogenum* remained as most resistant strain<sup>94</sup>.

### Antiviral activity

*P. emblica* contains different class of secondary metabolites<sup>47</sup>. Phyllaemblicin B extracted from plant roots showed inhibitory potential for Coxsackie virus<sup>53,95</sup> while phenolic content revealed effectiveness for herpes simplex viruses (HSV) 1 and 2<sup>96</sup>. 1, 2, 4, 6-tetra-O-galloyl- $\lambda$ -D-glucose from *P. emblica* showed antiviral activity for HSV *in vitro*<sup>96</sup>. Pentagalloylglucose inhibits influenza A virus replication by prevention of adsorption of the virus and suppressing release of virus<sup>97</sup>. Several plant extracts possess potential to act against HIV via inhibition of viral enzymes<sup>98</sup>. *P. emblica* plant extracts may have anti-HIV property

by inhibiting reverse transcriptase enzyme of the virus<sup>99</sup>. In this study, four solvents were for extraction (n-hexane, carbon tetrachloride, chloroform, aqueous fractions) among which aqueous and n-hexane fractions exhibited the highest inhibition of recombinant HIV reverse transcriptase enzyme at 1mg/ml concentration<sup>99</sup>.

Polyphenolic compound of EO may possess anti-HSV effects via inactivating extracellular viral particles and interfering viral biosynthesis of the host cells, thus might serve as a potential therapeutic candidate against HSV<sup>96</sup>. Evaluation of the effectiveness of EO extract towards transcriptional activity of human papilloma virus (HPV) revealed inhibition of DNA binding of activator protein-1 (AP-1) in both HPV16- and HPV18- positive cervical cancer cell lines<sup>100</sup>.

An overview on the antimicrobial activities and modes of action of *E. officinalis* is depicted in Fig. 1.

### Phytochemicals

Amla is a precious natural herb that helps maintain and rejuvenate health of humans in various aspects. The health beneficial phytochemicals and antimicrobial potentials of leaf, fruit and bark of amla are now widely proven. The oil extracted from seeds of amla showed antimicrobial activity

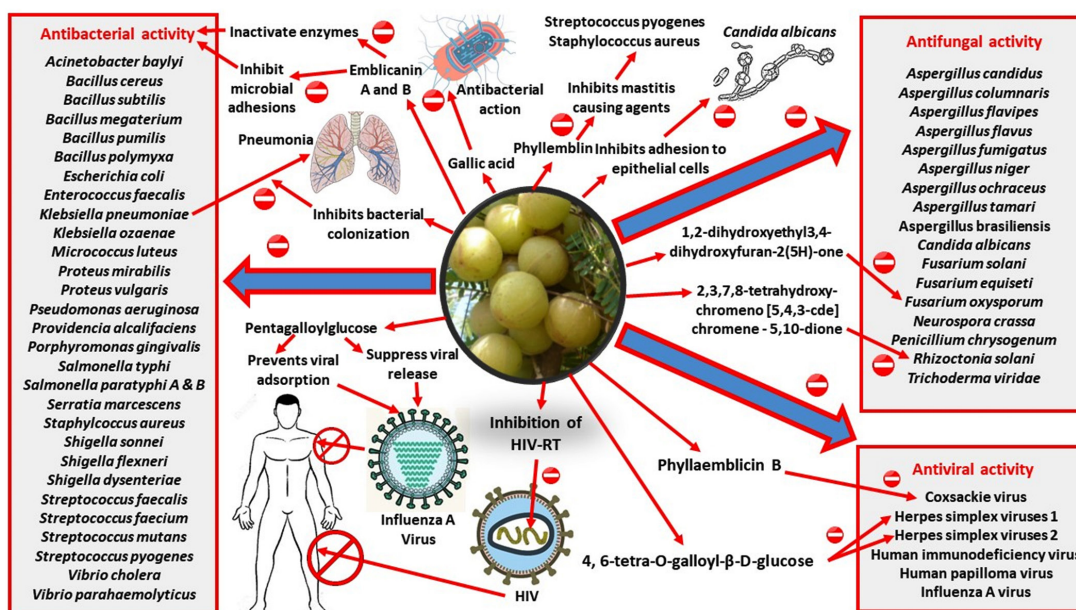


Fig. 1. Antimicrobial activity spectrum of *Emblica officinalis* and its modes of action

due to certain biologically active compounds. The crude extract obtained from seeds of amla revealed highest zone of inhibition with regards to antibacterial and antifungal actions as compared to regular drugs<sup>45</sup>. An attempt was made to identify the phytoconstituents in both aqueous and methanolic extracts of EO fruit thereby confirming their antibacterial and antifungal potentials. The aqueous extract contained the compounds 2,4-Di-tert-butylphenol (C<sub>14</sub>H<sub>22</sub>O) and Heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl (C<sub>14</sub>H<sub>44</sub>O<sub>6</sub>Si<sub>7</sub>) whereas the compound Phenol, 3,5-bis (1,1-dimethylethyl) (C<sub>14</sub>H<sub>22</sub>O) was identified from the methanolic extract<sup>74</sup>. Several important phytoconstituents have been identified in amla like ellagic and gallic acid, emblicanin A and B, quercetin, phyllantine and phyllantidine that possess well established biological actions like antioxidant, anti-inflammatory, antimicrobial, antidiabetic, antitussive, radioprotective, and chemopreventive effects which can be used to manage different diseases<sup>37</sup>. Several types of cultivars are available for *E. officinalis*. An attempt was made recently to assess physical and chemical characteristics of different cultivars (NA-7, NA-9, NA-10, Chakaiya, Balwant and Hathijhool) of Indian gooseberry. The study involved comparison of several important parameters like fruit size, volume, moisture content, textural characteristics, and proximate composition. The highest size of fruit was seen in NA-7 cultivar and highest density was seen in Hathijhool cultivar. The levels of ascorbic acid and polyphenol content were also evaluated with level being highest in the Chakaiya cultivar<sup>101</sup>. Hence we have to assume that the phytoconstituents levels may be subjected to change according to the type of cultivars used for the study.

Plant phytochemicals viz., saponins, alkaloids, flavonoids, tannin and other aromatic constituents acting as secondary metabolites provide defenses against several microorganisms<sup>17,102</sup>. Methanol and aqueous extracts of EO fruits revealed existence of alkaloids, tannins, saponins, steroids, phenols, glycosides and flavonoids. Hexane extracts possessed less phytochemicals compared with other extracts that is the cause for its lower antimicrobial actions<sup>90,103</sup>. Seventeen bioactive constituents viz., alcohol, saturated hydrocarbons, unsaturated fatty acid,

fatty alcohol, alkane hydrocarbons, vitamin E, ester compounds, plant sterols and triterpenes renders therapeutic potential to EO. Antimicrobial potential of EO may owe to secondary metabolites like 1-hexacosanol, octadecanoic acid, methyl ester, gamma-sitosterol and 12-oleanen-3-yl acetate<sup>104</sup>. Ethyl acetate extract was tested most effective by having higher contents of phytochemicals with significant antibacterial properties. Existence of more bioactive phytochemicals renders higher inhibitory effect to an extract<sup>62</sup>.

The *in vitro* antimicrobial potential analysis of *Emblica* essential oils (EOs), obtained by hydrodistillation (HD-EO) and supercritical fluid extraction (SFE-EO), with main components as β-caryophyllene, β-bourbonene, 1-octen-3-ol, thymol and methyleugenol, revealed EOs having broad spectrum effects against all bacterial and fungal agents examined. Gram-positive bacteria showed comparatively more sensitivity to EOs than Gram-negative bacteria. SFE-EO showed higher antifungal potential as compared to HD-EO<sup>105</sup>. Out of tannins, saponins, flavanoids and phenols present as phytochemicals in EO, the flavonoids and saponins exhibited most inhibitory effects against the pathogens examined<sup>67</sup>.

Phytochemical examination of EO revealed the presence of eblicannin, gallic, ellagic, chebulinic, chebulagic acids, quercetin<sup>81</sup>. The antimicrobial activity of EO and *M. arvensis* has been recognized because of hydrolysable tannins and menthol, respectively<sup>106</sup>. The fruit protein extracts showed antibacterial action for *S. aureus*, *B. cereus*, *B. subtilis* and *E. coli*<sup>107</sup>. Methanolic, ethanolic and ethyl acetate extracts of amla fruits and their powders were found to exhibit a powerful antimicrobial action for *E. coli*, *Salmonella typhi*, *S. aureus* and *C. albicans*<sup>108</sup>. Phenolic compounds form complexes with extracellular and soluble proteins or cell walls of bacteria, thus induce disruption in bacterial membrane<sup>109</sup>. The superior antimicrobial potential of EO fruit extract owes to the phenolic compounds others such as phenol, 3,5-bis (1,1-dimethylethyl), 2,4-Di-tert-butylphenol and heptasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13-tetradecamethyl<sup>74</sup>.

#### Mechanisms of action

Plant extracts possesses potent antimicrobial properties to counter Gram-positive bacteria, owing to differences of bacterial cell

wall structure (more complex in Gram-negative bacteria)<sup>110-112</sup>. Various modes of antimicrobial actions EO fruits juices are elucidated, although exact targets and mechanisms are not thoroughly understood. Antimicrobial potential is largely ascribed to polyphenols and organic acids<sup>113</sup>. Identifying the specific sites of action may be difficult for natural products owing to several interactive reactions occurring simultaneously<sup>114</sup>. Antibacterial compounds can destroy cell wall and cytoplasmic membrane of the bacteria, resulting in cytoplasm leakage and coagulation, damage proteins, interfere with enzymatic activities, adversely affect DNA and RNA synthesis, lead to disturb electron transport and nutrient uptake, impair energy production and fatty acids and phospholipid constituents are altered inside the cell<sup>115,116</sup>.

Antibacterial properties of EO extracts are mainly attributed to alkaloids, cardiac glucosides, saponins, tannins terpenoids, phenols and flavonoids<sup>67</sup>. Flavonoids inhibit RNA synthesis in microbes owing to their B-ring which participate in intercalation or hydrogen bonding with stacking of nucleic acid bases. Emblicanin A, B and their derivatives also crucially take part in rendering antimicrobial effects<sup>117</sup>. Gooseberry fruits possess high hydrolysable tannins such as emblicanin A and B, punigluconin, and pedunculagin<sup>118,119</sup>. Tannins inhibit extracellular microbial enzymes, lead to deprivation of substrate necessary for microbial growth or interferes with metabolism via inhibiting oxidative phosphorylation. Alkaloids such as phyllembin, flavonoids like kaempferol and phenolic constituents of ellagic and gallic acid have been reported<sup>120,121</sup>. Antimicrobial potential of gooseberry and wild apple owes to phenolic constituents and flavonoids<sup>17</sup>. Phenols control protein to lipid ratio, functioning of membrane and ion channels, while catechins disrupt membrane integrity of lipid bilayers. Kaempferol inhibits protein kinase C and possess high antibacterial properties for combating multidrug-resistant pathogens (MRSA and VRE)<sup>122,123</sup>. Alkaloids may affect genetic materials of the microbes to gain antimicrobial properties<sup>113</sup>.

A broad-spectrum antibacterial pattern in gooseberry and wild apple fruit extracts have been reported<sup>124,125</sup>, the juices and their particles showed superior effects against drug-resistant

variants *viz.*, MRSA, VRE and ESBLs. The attainment of drug resistance is not associated with increase innate virulence of microbe<sup>126</sup>. *E. officinalis* fruit decoction revealed highest antibacterial potential, and then by methanolic extract of its leaves. *S. aureus* was observed to be most sensitive followed by *S. pyogenes*, while *K. pneumoniae* got moderately inhibited due capsular polysaccharide surrounding interfering with antimicrobial effects of EO leaf and fruit extracts<sup>110</sup>.

#### **Amla: Antimicrobial nanoparticles**

The rising concerns of emerging microbial resistance for antibiotics has paved way for designing of antimicrobial nanoparticles (NPs) such as silver NPs (AgNPs) and selenium NPs (SeNPs)<sup>75,127</sup>. Biogenic production of AgNPs from the plant sources is getting popularity in the present scenario, this is mainly because of the low cost factor when compared to the conventional chemical synthesis method<sup>127</sup>. AgNPs are ever more being utilized in therapeutics and diagnosis owing to their typical physical, chemical and antibacterial properties. Many theories of antibacterial activity of colloidal silver solution are proposed, it can change permeability of cell membrane, affects release of lipopolysaccharides and membrane proteins, free radical accountable for membrane damage, and dissipation of proton motive force leading to collapse of membrane potential; but exact modes need to be yet fully elucidated<sup>128</sup>. The size of AgNPs formed also affects the antibacterial activity, smaller AgNPs with large surface area for communication show stronger antibacterial actions. Using plant sources for synthesis of AgNPs will be economic, less toxic, more effective, and also an environment friendly approach<sup>127,129</sup>. We can use fresh fruit extract of EO as a stabilizing, reducing, and capping agent in process of silver nanoparticle preparation<sup>127</sup>.

AgNPs have shown potent antimicrobial effects in countering *E. coli*, *S. aureus* and *S. marcescens*<sup>130-132</sup>. It also showed antinematode<sup>133</sup>, antiviral<sup>134</sup>, anticancer<sup>135,136</sup> and anti-inflammatory effects<sup>137</sup>. Aqueous *P. emblica* fruit extract when evaluated against eight pathogenic cultures and its applicability in green synthesis of AgNPs showed that all the test cultures were inhibited by the AgNPs and the average ZOI measured  $19.25 \pm 2.7$  mm<sup>129</sup>. The AgNPs produced from fresh aqueous EO fruit extract possessed antibacterial



effects for gram negative and positive bacteria. Evaluation of *P. emblica* methanolic seed extract and palladium nanoparticles (PdNPs) against four different pathogens revealed that seed extract had maximum ZOI against *B. subtilis* followed by *S. aureus*, while PdNPs had maximum ZOI against *S. aureus* followed by *P. aeruginosa*<sup>138</sup>. MIC results reflected *B. subtilis* to be inhibited at lower concentration for extract and PdNPs. The most resistant pathogen was found to be *P. mirabilis* as compared to other microbes<sup>138</sup>. Comparative studies of methanol extract and zinc oxide NPs revealed green synthesized zinc oxide NPs from EO to be effective antibacterial in traditional system of medicine<sup>139</sup>. The EO aqueous fruit extract has been used to produce phytofabricated selenium NPs (PF-SeNPs) by reducing it with sodium selenite<sup>75</sup>. The PF-SeNPs had antimicrobial activity against several food-borne pathogens. Due to this peculiarity it is having wide application in food and pharmaceutical industry. These PF-SeNPs have superior activity against fungi, and then for Gram positive and negative bacteria. Cytotoxicity study suggested PF-SeNPs to be safer and less toxic when compared to the sodium selenite<sup>75</sup>. In this study, PF-SeNPs exhibited concentration dependent antioxidant effect (directly proportional relationship between concentration of PF-SeNPs

and its corresponding antioxidant effect) along with effective antimicrobial properties for both bacterial and fungal pathogens.

Fresh fruit extract of EO has been utilized for synthesizing AgNPs. Based on *in vitro* antibacterial sensitivity test, it was found that the synthesized nanoparticle showed significant level of activity for bacteria *Acidovorax oryzae* strain RS-2, a pathological agent causing bacterial brown stripe in rice plant<sup>127</sup>. An attempt was made to incorporate plant extracts into nanofiber scaffold so that its biological functions can be modified. *E. officinalis* loaded poly(l-caprolactone) (PCL) nanofibers have been produced to incorporate antibacterial and anti-cancerous activity into the scaffold<sup>140</sup>. The nanofiber scaffold loaded with EO possessed remarkable antibacterial action for Gram positive and negative bacteria with greater antibacterial effect for Gram positive bacteria<sup>140</sup>. Such nanofiber scaffolds containing EO extracts can be considered as the suitable candidates for wound management in infected wounds and cancer patients.

#### Other potential health applications of Amla

The other beneficial health effects of *E. officinalis* comprise of anti-oxidative, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, anti-cancer, anti-mutagenic, cardioprotective, and

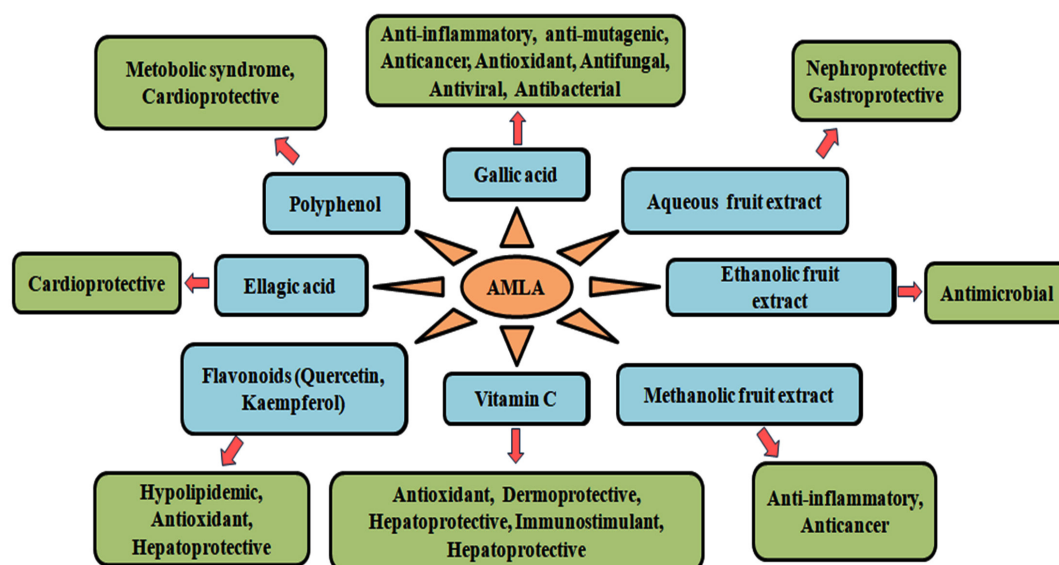


Fig. 2. Therapeutic activities of solvent extract and compounds of *Emblica officinalis*

hepatoprotective modes of action<sup>68,141-143</sup> (Fig. 2). Gallic acid equivalent as total phenolic substance of EO fruit and seed possesses remarkable antioxidant actions and as free radical scavengers necessary in maintaining redox homeostasis<sup>144</sup>. Methanolic seed extract of EO showed potent free radical scavenging property of 1, 1-Diphenyl-2-picrylhydrazil (DPPH) in a concentration dependant mode<sup>145</sup>. Saponins present in EO show insecticidal or cytotoxic activity against some of the insects<sup>146</sup>. The methanol extract of EO produced larvicidal and pupicidal activities combating malarial vector (*Anopheles stephensi*), presenting 98% mortality at 100 ppm<sup>147</sup>. Antidepressant potential of aqueous extract of EO fruits as assessed in inbred male Swiss albino mice (25-30g) revealed comparable effects with the drug imipramine, which suggest it to be a suitable candidate as an adjuvant in the treating several nervous disorders<sup>148</sup>. Water extract of EO showed inhibitory consequence on production and release of inflammatory mediators in rats<sup>149</sup>. EO extract treatment of mice previous to exposure of different doses of gamma radiation has been found to decrease magnitude of symptoms of radiation sickness and mortality<sup>150</sup>. Amla fruit also possesses remarkable antihyperlipidemic, hypolipidemic, and anti-atherogenic effect<sup>151</sup>. Efficacy trial of *P. emblica* aqueous fruit extract on triglycerides (TG) and liver-specific enzyme, alanine transaminase (ALT) levels, revealed that at a dose of 200 mg/kg body weight it significantly trim down blood glucose in alloxan induced diabetic rats<sup>152</sup>. The oral feeding of low dose EO extract in mice for two weeks resulted in significant increase in plasma free fatty acids which could be due to increased lipolysis or decreased adipose tissue lipid storage<sup>153</sup>. In a study conducted with chewing gum containing *P. emblica* fruit extract it was found that a short term use of the gum stimulates the salivary flow which altered the pH levels<sup>79</sup>. It also reduced the volatile sulfur compound concentrations which was critical in reducing the oral malodor.

*E. officinalis* has also been evaluated for its curative application against various neurodegenerative disorders like dementia, Alzheimer's disease and Parkinson's disease<sup>154</sup>. Phytochemicals such as quercetin, gallic acid, corilagin and ellagic acid in amla put forth

hepatoprotective effects to alleviate toxicity of paracetamol, microcystins, galactosamine and lipopolysaccharide. Such health protective actions owe to antioxidant, anti-inflammatory and hypolipidemic properties and modulating detoxifying enzymes<sup>155</sup>. EO also possesses powerful memory enhancing actions, reducing cholesterol levels and ameliorating ophthalmic disorder<sup>24</sup>. Prebiotics have been found effective in management of gut microbiota dysbiosis, however produce side effects during long period usage such as abdominal bloating and flatulence. As an option to prebiotics, EO extracts have been assessed for their potency in modulating gut microflora, high dose of oral supplementation caused increased microbial quantity of *Eubacterium* genus of *Eubacteriaceae* family, however overall microbial diversity was not affected<sup>153</sup>.

In Ayurvedic medicine, Amla oil has been used for its beneficial roles in hair nourishment and as scalp tonic<sup>10,156,157</sup>. It has also been investigated for its antimicrobial and therapeutic purposes to combat several diseases and disorders including the deadly malady of cancers<sup>15,18,23,157</sup>. Anticancer modes of actions of Amla comprise of free radical and antioxidant properties, modulation of inflammatory enzymes, carcinogenesis, and cell cycle proteins, induction of apoptosis in neoplastic cells, and preventing the process of metastasis<sup>158</sup>. *E. officinalis* seed extract has been found to induce cell death in human cervical cancer cells, thus making it a suitable candidate for its treatment<sup>138</sup>. Antiproliferative activity of extracts of Indian gooseberry was also observed<sup>159</sup>. Promising anti-plasmodial effectiveness observed in the EO leaf extracts may serve for their utility as antimalarial agents even in crude form, and also to be even effective against Chloroquine-resistant strains<sup>160</sup>. The extracts of EO expressed *in vivo* anti-plasmodial effects with appropriate suppression ranging from 53.40 to 69.46%<sup>161</sup>. Chyawanprash is a commercially available brand of Ayurvedic health supplement that is available throughout the India. It is concentrate made up of several herbs and minerals. *E. officinalis* is an important herbal component of chyawanprash due to its immunomodulatory, rejuvenative, neuroprotective, hepatoprotective, antioxidant, and cardiotoxic activity. It also

enhances the general vitality and cognitive function in the consumers<sup>162</sup>. The constituents that are responsible for these activities are 6-ethenyl-4,5,6,7-tetrahydro-3,6-dimethyl-5-isopropenyl-trans-benzofuran, 8,9-dehydro-9-formyl-cycloisolongifolene,  $\gamma$ -elemene and eucalyptol<sup>162</sup>.

Multiple beneficial health applications including the potent antimicrobial properties, medicinal and therapeutic values of *Emblica officinalis* need to be promoted and propagated with more researches and clinical trials, validation studies, promotional activities along with exploration of advances in biotechnology, pharmacology, pharmaceuticals, nanotechnology based approaches for developing effective drugs and medicines utilizing Amla<sup>6,15-17,24,75,139,163-165</sup>. Particularly, in the scenario of rising drug resistance, higher incidences of emerging and re-emerging pathogenic microbes, the antimicrobial efficacy of *Emblica officinalis* can be exploited for important microbial pathogens including food-borne zoonotic bacteria such as Salmonella, Arcobacters, Camyprobacters, and emerging viral pathogens like Zika, Ebola, Nipah virus and others, so as to lessen their high incidences, devastating effects and public health effects; since various other herbs and plant metabolites / extracts have shown promising results against such pathogens<sup>5,6,166-169</sup>.

## CONCLUSION

Researchers are now trying to fill the lacunae of conventional drugs by exploring the traditional medicinal herbs. *Emblica officinalis* is a well recognized herb in Indian indigenous system of medicine. Different types of extracts and herbal formulations derived from Amla have shown tremendous therapeutic and beneficial health effects in countering several diseases and disorders. Several well established activities have been credited to the EO extracts which include antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, cryoprotective, antiaging, nephrotoxicity modulation, antidiabetic, hepatoprotective, anti-hyperlipidemic, insecticidal, anti-cancer, anti-atherogenic, anti-proliferative, anti-diarrheal, immunomodulator, gastroprotective, cardioprotective, neuroprotective, and radio-protective activity.

Even though several researches for qualitative analysis of phytochemicals has been done, further quantitative analysis of EO extracts for potent phytochemicals is necessary especially for assessment of their antimicrobial potential. Exploring the various mechanisms of action owing to antibacterial potential of specific compounds / constituents present in the plant extracts, would pave way forward for more usages of such natural herbs for countering microbial pathogens in an effective way by developing potent antimicrobial drugs and medicines as well as to alleviate the problem of emerging antimicrobial resistance. Appropriate actions must be taken to continue studies for designing and development of natural products from Amla for safeguarding various health issues. Another paramount research importance should aim to identify the phytochemical constituents of EO extract rendering specific activities. This will enable us to synthetically produce the identified active ingredient at a large scale so that further studies can be conducted to develop new commercial drugs that are basically originated from the natural sources.

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The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

All authors contributed significantly and equally.

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## ETHICS STATEMENT

The manuscript has been drafted with full responsibility, following due ethical

procedure, and there is no duplicate publication, fraud, plagiarism, or concerns about animal or human experimentation while maintain research compilation integrity.

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