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Review Article

Ethyl Protocatechuate: Integrative Perspectives On Its Chemistry, Molecular Pharmacology, Signaling Networks, Organ-Protective Activities, And Translational Potential As A Multi-Target Therapeutic Scaffold

Bijesh Vatakkeel[1], Haritha M.S.[2], Nesla P. P.[3]

[1]*Department of Pharmacology, College of Pharmaceutical Sciences Government Medical College Kannur, Kerala, India.*
[2]*Department of Pharmacology, College of Pharmaceutical Sciences Government Medical College Kannur, Kerala, India.*
[3]*Department of Pharmacology, College of Pharmaceutical Sciences Government Medical College Kannur, Kerala, India*

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ABSTRACT

Ethyl protocatechuate (EPC; ethyl 3,4-dihydroxybenzoate) is a naturally occurring catechol-containing phenolic ester that has recently emerged as a mechanistically diverse bioactive scaffold with considerable translational potential. Structural esterification of protocatechuic acid enhances lipophilicity while preserving its redox-active pharmacophore, thereby broadening its pharmacodynamic profile. Beyond its antioxidant capacity, EPC functions as an intracellular iron chelator and prolyl hydroxylase inhibitor, orchestrating HIF-1α-dependent cytoprotective signaling alongside modulation of NF-κB-mediated inflammation, mitochondrial homeostasis, extracellular matrix remodeling, apoptosis, angiogenesis, and oxidative stress responses. This review critically consolidates current evidence regarding the natural occurrence, chemistry, physicochemical characteristics, biotransformation, molecular mechanisms, pharmacological activities, toxicity profile, and translational prospects of EPC. Experimental findings demonstrate broad-spectrum antibacterial, antiviral, antifungal, anticancer, anti-inflammatory, antifibrotic, hepatoprotective, neuroprotective, cardioprotective, antiulcer, photoprotective, and anti-ageing activities. Nevertheless, the existing evidence remains predominantly preclinical, with substantial deficiencies in pharmacokinetic characterization, comprehensive toxicological

***Corresponding Author:** Haritha M.S.
Address: *Department of Pharmacology, College of Pharmaceutical Sciences Government Medical College Kannur, Kerala, India*
Email ✉: harithasajeevkumar@gmail.com
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evaluation, clinical validation, and mechanistic elucidation for several therapeutic indications. By integrating fragmented evidence, this review identifies EPC as a promising multi-target pharmacophore and delineates critical research priorities required to facilitate its rational development as a next-generation multi-organ therapeutic agent.

1. INTRODUCTION

Natural products have long provided the molecular scaffolds that underpin modern pharmacotherapy, with phenolic compounds representing a particularly important class of bioactive molecules due to their broad therapeutic potential.[1] Among these, natural phenolic acids and their derivatives have attracted considerable scientific interest because of their broad spectrum of biological activities, including antioxidant, anti-inflammatory, antimicrobial, and cytoprotective effects. Their ability to modulate multiple pathological processes, particularly those driven by oxidative stress and inflammation, further underscores their potential as promising candidates for the prevention and treatment of chronic diseases.[2,3] Efforts to structurally modify naturally occurring phenolic acids have been extensively pursued to optimize physicochemical properties and enhance therapeutic performance.[4]

Ethyl protocatechuate (EPC) is a naturally occurring phenolic ester initially isolated and structurally characterized from peanut *(Arachis hypogaea)* seed testa, where it was identified as one of the principal antioxidant constituents responsible for suppressing lipid peroxidation.[5] EPC has gained increasing attention due to its strong antioxidant capacity and promising pharmacological and therapeutic potential.[5,6] In addition to its occurrence in natural sources, EPC can be synthesized by esterification of protocatechuic acid, a strategy widely employed to prepare protocatechuic acid alkyl esters for obtaining sufficient quantities for investigating their physicochemical and pharmacological properties.[7,8]

EPC is the ethyl ester derivative of PCA, retaining the catechol moiety that contributes substantially to the antioxidant properties of both compounds.[9] Esterification of PCA modifies the physicochemical properties of the molecule, particularly by increasing lipophilicity, while preserving the phenolic structure responsible for radical-scavenging activity.[7] This structure-property relationship, together with the reported antioxidant and other pharmacological effects of EPC, provides a rationale for investigating its broader therapeutic potential as a bioactive phenolic ester.[5,7]

Although many experimental investigations have explored specific pharmacological effects of EPC, an integrated review covering its natural sources, chemical structure, molecular mechanisms and targets, pharmacological actions, toxicity, and therapeutic potential is still scarce. This article therefore seeks to provide a critical synthesis of current reports, highlighting EPC's translational relevance in drug discovery. By integrating current evidence, this review critically evaluates the pharmacological potential, molecular mechanisms, safety profile, and translational prospects of EPC, while identifying key knowledge gaps and future research priorities for its development as a multi-organ therapeutic candidate.

2. ETHYL PROTOCATECHUATE

Ethyl protocatechuate, also known as ethyl 3,4-dihydroxybenzoate, is a naturally occurring phenolic ester derived from protocatechuic acid (PCA; 3,4-dihydroxybenzoic acid).[5] Ethyl protocatechuate (EPC), also reported in the literature under the synonymous designations ethyl 3,4-dihydroxybenzoate (EDHB) and

dihydroxybenzoic acid ethyl ester (DHB), is here referred to uniformly as EPC throughout this review.

3. NATURAL SOURCES OF ETHYL PROTOCATECHUATE

The natural occurrence of EPC is well-documented across taxonomically diverse plant sources. EPC has been isolated and structurally characterized in the seed testa of peanut *Arachis hypogaea*[5], subsequently detected among the chemically profiled secondary metabolites of the seagrass *Halodule pinifolia*[10], and further identified as a bioactive constituent in *Duchesnea indica* extracts exhibiting anti-hepatocellular carcinoma activity.[11] These findings highlight EPC's widespread distribution as a phenolic ester across taxonomically distinct species, reinforcing its role as a naturally occurring bioactive metabolite with pharmacological relevance.

4. CHEMISTRY AND STRUCTURAL CHARACTERISTICS

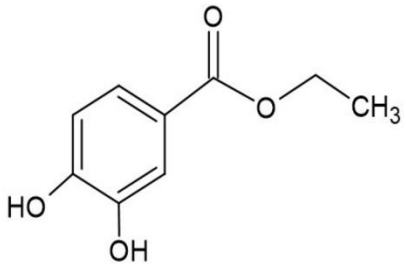

Figure 1: Chemical structure of ethyl protocatechuate (EPC). Created by the authors using ChemSketch. [12]

As illustrated in Figure 1, EPC is an aromatic phenolic ester generated by esterification of the carboxyl group of protocatechuic acid with an ethyl moiety.[13,7] Structurally, it comprises a catechol-substituted benzene ring bearing hydroxyl groups at the 3 and 4 positions and an ethyl ester group, forming a catechol-benzoate framework.[13] The catechol hydroxyl groups confer hydrogen-bonding capability, whereas esterification increases lipophilicity relative to PCA,[7] potentially enhancing membrane permeability and its antioxidant and pharmacological activities.[5]

5. PHYSICAL PROPERTIES

EPC ($C_9H_{10}O_4$; molecular weight 182.17 g/mol) is a low-molecular-weight phenolic ester that occurs as a white to pale yellow crystalline solid with a melting point of 132-135°C. Owing to its esterified aromatic framework, EPC exhibits poor aqueous solubility but readily dissolves in organic solvents, particularly ethanol, reflecting its enhanced lipophilic character relative to protocatechuic acid.[13]

6. BIOTRANSFORMATION AND URINARY EXCRETION OF EPC

Direct pharmacokinetic investigations of pure EPC remain limited. However, human xenobiotic metabolism studies have identified EPC as a hydroxylated metabolite of ethyl paraben, generated through oxidative biotransformation. Following its formation, EPC undergoes extensive phase II metabolism, predominantly glucuronidation and sulfation, facilitating efficient

renal elimination. Human biomonitoring studies have consistently demonstrated a strong correlation between urinary concentrations of EPC and its parent compound, indicating that EPC is a robust urinary biomarker of ethyl paraben exposure and confirming hydroxylation followed by conjugative metabolism as a major metabolic pathway in humans.[14]

7. EXPERIMENTAL AND MECHANISTIC INSIGHTS

7.1. Iron Chelation, Prolyl Hydroxylase Inhibition, and HIF Signaling

EPC exerts part of its pharmacological activity by modulating cellular iron homeostasis. Its catechol moiety chelates intracellular iron, inducing functional iron deficiency and activating the iron-responsive element/iron regulatory protein (IRE/IRP) pathway, thereby increasing transferrin receptor expression, suppressing ferritin synthesis, and altering cellular iron metabolism.

Furthermore, EPC chelates the catalytic iron required for prolyl-4-hydroxylase activity, inhibiting this iron-dependent enzyme and consequently modulating collagen biosynthesis and hypoxia-inducible factor (HIF)-related signaling. Collectively, iron chelation and prolyl hydroxylase inhibition are key mechanistic determinants of EPC's biological actions and may contribute to its reported organ-protective and therapeutic effects, although current evidence is largely limited to in vitro studies.[15]

7.2. HIF-1α-VEGF mediated angiogenesis and anti-apoptotic effects

EPC exerts cytoprotective effects by inhibiting hypoxia-inducible factor prolyl hydroxylase (PHD), thereby stabilizing HIF-1α and enhancing VEGF-mediated angiogenesis. In a rabbit model of steroid-induced osteonecrosis, EDHB reduced osteocyte apoptosis through upregulation of Bcl-2 and downregulation of caspase-3, improved bone microvascularization, and preserved trabecular architecture, highlighting the therapeutic relevance of the PHD-HIF-1α-VEGF signaling pathway in tissue protection and regeneration.[16]

7.3. Prolyl Hydroxylase Inhibition and Collagen-Mediated Regulation of Myogenesis

EPC is a valuable mechanistic probe for investigating collagen biosynthesis, cellular differentiation, and extracellular matrix (ECM) remodeling. As a competitive inhibitor of prolyl-4-hydroxylase, EPC prevents proline hydroxylation during collagen maturation, producing under-hydroxylated procollagen that fails to form stable triple helices and is degraded intracellularly rather than secreted. Consequently, EPC suppresses hydroxyproline synthesis, procollagen secretion, ECM deposition, and expression of the collagen-associated chaperone gp46, despite upregulating procollagen α1(I) and α2(I) mRNA, indicating a predominantly post-translational mechanism. These alterations reversibly impair early myogenic differentiation, including cell alignment, myoblast fusion, and muscle-specific gene expression, underscoring the critical role of collagen maturation in skeletal muscle development. Collectively, EPC serves as a robust experimental tool for elucidating collagen metabolism, extracellular matrix biology, and collagen-dependent cellular differentiation.[17]

8. MAJOR PHARMACOLOGICAL ACTIVITIES

8.1. Antibacterial activity: EPC exhibits promising in vitro antibacterial activity against clinically relevant *Staphylococcus aureus*, including methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) strains. MIC values

ranging from 64–1024 µg/mL against 20 clinical isolates and three reference strains demonstrate broad-spectrum inhibitory activity independent of methicillin or MLSB resistance phenotypes. Although the precise antibacterial mechanism remains unclear, EPC displays intrinsic antimicrobial activity against both susceptible and multidrug-resistant *S. aureus*, highlighting its potential as a natural antibacterial scaffold for combating resistant staphylococcal infections.[18]

Further studies demonstrated that EPC enhances the activity of erythromycin against *S. aureus* and Staphylococcus epidermidis in a strain-dependent manner. Checkerboard and fractional inhibitory concentration (FIC) analyses revealed synergistic or additive interactions in several isolates, particularly multidrug-resistant strains, with significant reductions in erythromycin MIC values. These findings suggest that EPC may potentiate antibiotic efficacy by sensitizing resistant bacteria and modulating resistance mechanisms. Collectively, current evidence supports EPC as a promising antibiotic adjuvant for improving therapy against resistant staphylococcal pathogens, although mechanistic investigations and *in vivo* validation remain necessary.[19]

8.2. Anticancer activity: EPC exhibits potent anticancer activity by suppressing tumor cell proliferation through coordinated induction of cell cycle arrest, apoptosis, and autophagy. In human esophageal squamous cell carcinoma (KYSE170 and EC109) cells, EPC inhibited proliferation in a dose- and time-dependent manner, induced S-phase arrest, disrupted mitochondrial membrane potential, and activated the intrinsic apoptotic pathway via caspase-9 and caspase-3 cleavage. Mechanistically, EPC inhibits prolyl hydroxylase, stabilizing hypoxia-inducible factor-1α (HIF-1α) and subsequently upregulating BNIP3, Beclin-1, and N-myc downstream-regulated gene-1 (NDRG1), thereby promoting mitochondrial dysfunction, BNIP3/Beclin-1-mediated autophagy, and apoptosis. Silencing NDRG1 markedly attenuated EPC-induced apoptosis, confirming its pivotal role in the underlying anticancer mechanism.[20]

The anticancer efficacy of EPC has been further enhanced through solid lipid nanoparticle (SLN)-based delivery. EPC-loaded SLNs exhibited superior antiproliferative activity against CaCo-2 colorectal cancer cells compared with free EPC while demonstrating negligible cytotoxicity toward normal human fibroblasts. This enhanced therapeutic effect is attributed to improved cellular uptake, sustained drug release, and increased membrane permeation, indicating that nanocarrier-mediated delivery may overcome pharmacokinetic limitations and strengthen the translational potential of EPC as a selective anticancer agent.[21]

8.3. Antioxidant activity: EPC exerts potent antioxidant effects by protecting cells from hypoxia- and oxidative stress-induced injury through activation of hypoxia-inducible factor-1α (HIF-1α) signaling. As a competitive inhibitor of prolyl hydroxylase domain (PHD) enzymes, EPC stabilizes HIF-1α, upregulating cytoprotective antioxidants, including heme oxygenase-1 (HO-1) and metallothioneins. This response attenuates lipid peroxidation and protein oxidation while restoring intracellular glutathione (GSH) levels and enhancing endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), thereby improving cellular resistance to hypoxic injury.[22]

EPC also protects fibroblasts against ultraviolet B (UVB)-induced oxidative damage by suppressing NADPH oxidase-mediated reactive oxygen species (ROS) generation, preserving

mitochondrial membrane potential, reducing lipid peroxidation and DNA damage, and restoring catalase (CAT), SOD, and GSH levels. Moreover, EPC inhibits nuclear factor-κB (NF-κB) activation and downregulates cyclooxygenase-2 (COX-2), matrix metalloproteinase-1 (MMP-1), and MMP-9, thereby preventing UVB-induced photodamage and photoaging. Collectively, EPC mediates antioxidant protection through both direct free radical scavenging and modulation of cellular redox signaling pathways.[23]

8.4. Antiulcer activity: Kore et al. evaluated the antiulcer efficacy of EPC in Wistar albino rats (200–250 g) using pylorus ligation-, aspirin-, and ethanol-induced gastric ulcer models. EPC (30 and 60 mg/kg, i.p.) was administered 30 min before ulcer induction, with ranitidine or sucralfate as reference drugs. EPC significantly reduced ulcer formation in all models in a dose-dependent manner, with the 60 mg/kg dose providing greater gastroprotection (48.80%, 65.11%, and 52.48% in pylorus ligation-, aspirin-, and ethanol-induced ulcers, respectively). In pylorus-ligated rats, EPC also decreased gastric juice volume, free and total acidity, and pepsin activity. Although less potent than the standard drugs, EPC exhibited significant gastroprotective activity, likely mediated through suppression of gastric secretory factors and enhancement of mucosal defense and cytoprotection.[24]

8.5. Neuroprotective activity: EPC exhibits neuroprotective potential by modulating hypoxia-responsive and inflammatory signaling. In a rat model of acute hypobaric hypoxia, EPC pretreatment reduced cerebral vascular leakage and brain edema while suppressing NF-κB activation, pro-inflammatory cytokines, cell-adhesion molecules, and vascular endothelial growth factor (VEGF). These effects were associated with HIF-1α stabilization and upregulation of cytoprotective proteins, including heme oxygenase-1 (HO-1) and metallothionein, suggesting preservation of blood–brain barrier integrity and attenuation of hypoxia-induced neuroinflammation.[25]

Electrophysiological studies in rat hippocampal preparations further demonstrated concentration-dependent, reversible modulation of synaptic transmission without compromising neuronal viability, although higher concentrations impaired synaptic plasticity, indicating dose-dependent effects on neuronal signaling.[26]

Collectively, current evidence indicates that EPC confers neuroprotection through HIF/PHD modulation, antioxidant and cytoprotective mechanisms, suppression of NF-κB-mediated neuroinflammation, preservation of blood–brain barrier integrity, and regulation of neuronal stress signaling. However, validation in disease-specific neurological models and comprehensive pharmacokinetic, CNS exposure, and long-term safety studies remain necessary.[25,26]

8.6. Hepatoprotective activity: EPC exhibits hepatoprotective activity in a murine hepatic ischemia–reperfusion (I/R) injury model. Pretreatment with EPC (100 mg/kg, i.p.) activated the prolyl hydroxylase–hypoxia-inducible factor-1α (PHD–HIF-1α) pathway and upregulated heme oxygenase-1 (HO-1), thereby attenuating mitochondrial permeability transition, mitochondrial membrane depolarization, reactive oxygen species (ROS)-mediated lipid peroxidation, hepatocellular necrosis, and serum alanine aminotransferase (ALT) elevation. Pharmacological inhibition of HO-1 partially abolished these protective effects, confirming the pivotal role of the HIF-1α/HO-1 axis in EPC-mediated hepatoprotection. Collectively, EPC protects against hepatic I/R injury by preserving

mitochondrial integrity and suppressing oxidative stress.[27]

8.7. Anti-inflammatory activity: EPC was identified in Halodule pinifolia extract, which reduced TNF-α, IL-1β, and IL-6 levels in lipopolysaccharide (LPS)-induced inflammation and carrageenan-induced paw oedema models. However, as purified EPC was not evaluated independently, these findings provide supportive rather than conclusive evidence for its anti-inflammatory activity.[10]

In UVB-irradiated L929 fibroblasts, purified EPC (P2) exerted direct anti-inflammatory and photoprotective effects by improving cell viability and attenuating lipid peroxidation, mitochondrial dysfunction, and DNA damage. Mechanistically, EPC suppressed NF-κB p65 nuclear translocation and downregulated matrix metalloproteinase-1 (MMP-1), MMP-9, and cyclooxygenase-2 (COX-2), indicating that its anti-photoaging activity is mediated through inhibition of oxidative stress, NF-κB-dependent inflammation, and extracellular matrix degradation.[23]

8.8. Cardioprotective activity: EPC exhibits cardioprotective activity by activating a prolyl hydroxylase-dependent cytoprotective pathway in isolated rabbit cardiomyocytes. Its effects involve nitric oxide synthase (NOS)-mediated NO-cGMP signaling and controlled mitochondrial reactive oxygen species (ROS) generation, as pharmacological inhibition of NOS or guanylyl cyclase significantly attenuated EPC-induced ROS signaling. These findings indicate that EPC functions as a hypoxic mimetic capable of pharmacologically preconditioning the myocardium and activating endogenous cardioprotective mechanisms.[28]

EPC further demonstrated dose-dependent cardioprotection in a doxorubicin (DOX)-induced acute cardiotoxicity model. Oral pretreatment (50–150 mg/kg) attenuated DOX-induced tachycardia, myocardial injury biomarkers (LDH, AST, and CK-MB), cardiac hypertrophy, and histopathological damage, with the greatest protection observed at 150 mg/kg. EPC also restored myocardial redox homeostasis by reducing malondialdehyde (MDA) levels and enhancing ferric-reducing antioxidant power (FRAP). Collectively, these findings suggest that EPC mitigates DOX-induced cardiac injury through its antioxidant, iron-chelating, and cytoprotective properties, supporting its potential as a cardioprotective therapeutic candidate.[29]

8.9. Antifungal activity: *In vitro* antifungal activity was evaluated using the CLSI M38-A2 broth microdilution method against Trichophyton rubrum and T. mentagrophytes, with MIC and MFC determined by spectrophotometric and subculture-based assays, respectively. Among the tested alkyl protocatechuates, EPC demonstrated moderate antidermatophytic activity, with MIC values of 31.2 mg/L against both *T. rubrum* and *T. mentagrophytes*, while the corresponding MFC values ranged from 31.2 to 125 mg/L. However, the longer-chain derivatives exhibited markedly greater fungicidal potency, indicating that increased alkyl-chain hydrophobicity enhanced antifungal activity.[30]

8.10. Anti-ageing and Photoprotective potential: EPC (P2) exerts potent anti-photoaging effects by protecting L929 fibroblasts against UVB-induced oxidative, mitochondrial, genotoxic, inflammatory, and extracellular matrix (ECM) damage. EPC attenuated lipid peroxidation, preserved mitochondrial membrane potential, and reduced DNA fragmentation and apoptotic nuclear changes, indicating protection against oxidative cellular injury. Mechanistically, EPC inhibited NF-κB p65 nuclear translocation,

resulting in downregulation of matrix metalloproteinase-1 (MMP-1), MMP-9, cyclooxygenase-2 (COX-2), and collagenase/elastase activities. Collectively, EPC suppresses the oxidative stress–NF-κB–matrix metalloproteinase axis, thereby preventing collagen and elastin degradation and mitigating UVB-induced cutaneous photoaging.[23]

8.11. Antiviral activity: EPC exhibited direct in vitro antiviral activity against Influenza A virus A/Vietnam/1194/2004 (H5N1) in Madin-Darby canine kidney (MDCK) cells, demonstrating a half-maximal inhibitory concentration (IC_{50}) of 16.11 µM, a cytotoxic concentration (CC_{50}) exceeding 169.99 µM, and a selectivity index (SI) >10.55. The pronounced separation between antiviral efficacy and cellular cytotoxicity provides preliminary evidence of a favourable in vitro antiviral therapeutic window for EPC against the highly pathogenic H5N1 strain. Nevertheless, although these findings substantiate the direct antiviral potential of EPC, the precise molecular and intracellular mechanisms underlying its inhibitory activity against H5N1 replication were not directly elucidated in the reported study.[31]

8.12. Antifibrotic activity: EPC exhibits antifibrotic potential by suppressing collagen biosynthesis through inhibition of prolyl-4-hydroxylase, the enzyme essential for 4-hydroxyproline formation and collagen triple-helix stabilization. In human normal and keloid fibroblasts, EPC (0.4 mM) reduced collagen synthesis to approximately 26–28.5% of control levels and markedly impaired type I and III procollagen synthesis and secretion without altering procollagen mRNA expression, indicating a predominantly post-translational mechanism. Importantly, these effects occurred independently of cytotoxicity or inhibition of global protein synthesis, supporting selective disruption of collagen maturation. Collectively, prolyl-4-hydroxylase inhibition represents a key molecular mechanism underlying the antifibrotic activity of EPC, although validation in relevant in vivo fibrosis models is still required.[32] An overview of the reported pharmacological activities of EPC is presented in Figure 2.

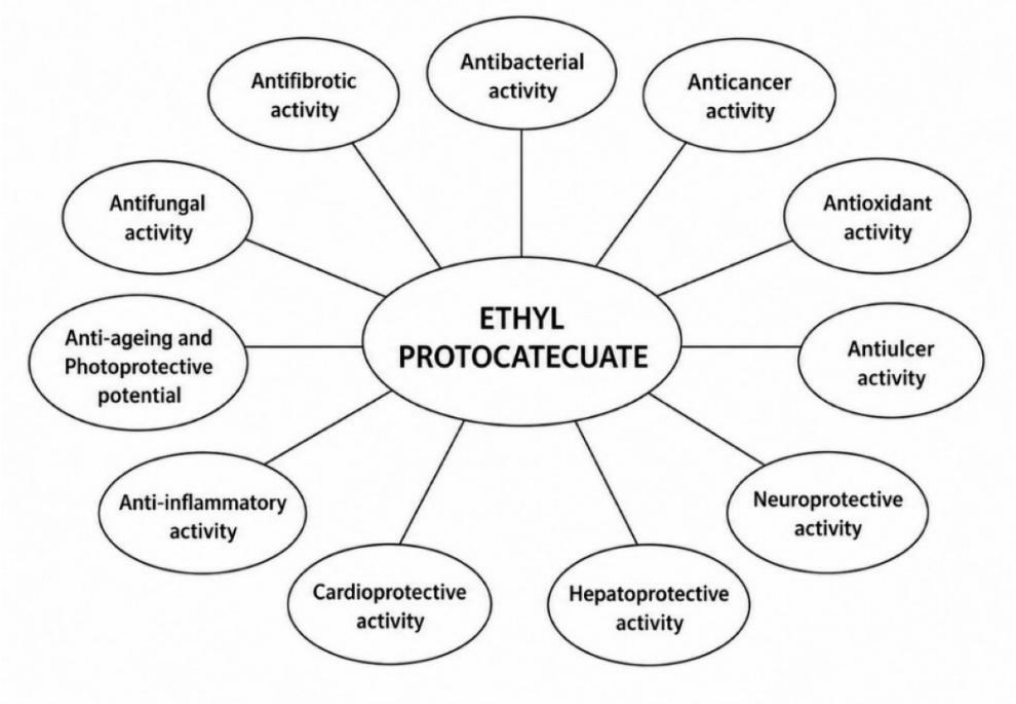

Figure 2: Pharmacological activities of ethyl protocatechuate (EPC). Created by the authors based on data compiled from published studies.[10,18-32]

9. EMERGING PHARMACOLOGICAL ACTIVITIES

9.1. Anti-tumour efficacy: EPC, isolated from Duchesnea indica, was identified by mass spectrometry as a principal bioactive constituent responsible for anti-hepatocellular carcinoma (HCC) activity. Network pharmacology and molecular docking demonstrated high-affinity interactions with key oncogenic regulators, including FOS, SERPINE1, AKR1C3, and FGF2, implicating modulation of apoptosis, angiogenesis, inflammation, and proliferative signaling. Functionally, EPC contributed to dose-dependent apoptosis, inhibition of migration, invasion, and angiogenesis in HCC cells, while significantly suppressing tumour growth with reduced Ki67 and CD34 expression in xenograft models. Transcriptomic analyses further revealed enrichment of p53-, apoptosis-, and angiogenesis-related pathways, highlighting EPC as a multi-target bioactive scaffold with promising therapeutic potential against HCC.[11]

9.2. Nephroprotective potential: The nephroprotective potential of EPC has been indirectly demonstrated in an oxalate-induced renal injury model using an ethyl acetate extract of Halodule pinifolia containing EPC (0.76 mg/g dry extract). The extract attenuated renal injury by reducing oxidative stress and inflammation, evidenced by significant decreases in blood urea nitrogen (BUN), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and kidney injury molecule-1 (KIM-1). However, as purified EPC was not evaluated independently, its direct nephroprotective efficacy remains unconfirmed and warrants further investigation.[10]

10. TOXICITY PROFILE OF ETHYL PROTOCATECHUATE

Preliminary 14-day oral repeated-dose studies suggest apparent tolerability of EPC at doses up to 150 mg/kg; however, its toxicological profile remains inadequately characterized. Comprehensive OECD-compliant acute and repeated-dose studies incorporating hematological, biochemical, histopathological, genotoxic, reproductive, and organ-specific endpoints are therefore warranted to define the safety margin and translational potential of EPC.[29]

11. RESEARCH GAP AND FUTURE PERSPECTIVES

Despite the broad pharmacological potential of ethyl protocatechuate (EPC), several therapeutic applications remain insufficiently explored. Direct experimental evidence for its **antidiabetic activity** is currently lacking, while its **analgesic effects** have not been adequately established. Likewise, the **antiatherosclerotic** and **antihyperlipidemic** potential of EPC remains unverified, although these activities are mechanistically plausible based on its structural relationship to PCA and its documented antioxidant, anti-inflammatory, endothelial-protective, and lipid-regulatory properties.[33,34,35] These gaps underscore the need for systematic preclinical and clinical investigations to fully define the therapeutic profile of EPC.

12. CONCLUSION

Ethyl protocatechuate (EPC) has emerged as a mechanistically versatile phenolic ester with considerable promise as a multi-target pharmacological scaffold. Current evidence

demonstrates that EPC exerts diverse organ-protective effects through integrated modulation of oxidative stress, inflammation, mitochondrial function, apoptosis, extracellular matrix remodeling, iron homeostasis, and hypoxia-responsive signaling, particularly via prolyl hydroxylase inhibition and HIF-1α-dependent pathways. These pleiotropic mechanisms underpin its reported antibacterial, antiviral, anticancer, antifibrotic, hepatoprotective, neuroprotective, cardioprotective, antiulcer, antioxidant, and photoprotective activities. Nevertheless, the available evidence remains predominantly preclinical, with substantial deficiencies in pharmacokinetic characterization, comprehensive toxicological evaluation, molecular target validation, and well-designed clinical investigations. Furthermore, several therapeutically relevant indications, including nephroprotective, antidiabetic, analgesic, antiatherosclerotic, and antihyperlipidemic activities, require direct experimental confirmation. Collectively, the available literature positions EPC as a promising lead compound for multi-organ therapeutic development. Future multidisciplinary studies integrating systems pharmacology, omics-based target identification, advanced drug-delivery strategies, and rigorous clinical translation will be essential to fully elucidate its therapeutic potential and establish EPC as a next-generation pharmacological candidate for precision medicine.

13. CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this manuscript.

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