CATECHOL: IMPORTANT SCAFOLD IN MEDICINAL CHEMISTRY

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ABSTRACT

The catechol scaffold is a significant structural component in medicinal chemistry since it is present in many naturally occurring compounds with varied biological effects, such as those that are anti-cancer, anti-inflammatory, antioxidant, anti-diabetic, antimicrobial, antiviral, and antifungal. Additionally, several other synthetic catechol motifs can be found in marketed drugs. They also play a part in a variety of physiological procedures and infection defence. This review will provide an overview of catechol moieties with medical applications synthesised in the previous 15 years by choosing the most effective compound from each publication. In this review, many methods for producing catechol and its derivatives have been discussed.

Keywords: Catechol, Synthetic methods of coumarin, Anticancer, Antioxidant, Anti-inflammatory, Biological activity.

INTRODUCTION

One of the fundamental building blocks of organic synthesis, catechol is produced on a massive scale to act as a precursor to medications, perfumes, and pesticides [1, 2]. Since then, scientists have learned that catechol exists naturally and unprocessed in kino and beechwood tar. Its sulfonic acid has been found to be present in both human and horse urine. Having two hydroxyl groups linked to nearby carbons, a catechol is a dihydroxyphenol. It has a phenolic group, a six-carbon unsaturated ring [3, 4]. The storage of transition metal ions and the watery adherence of marine organisms are just two biological processes that caterchols are involved in widely throughout nature. This is made feasible by the rich redox chemistry capabilities of the vicinal hydroxyl groups and the variety of interactions they have with surfaces of all sizes and shapes that have remarkably unique chemical and physical characteristics [5, 6].

PHYSICAL PROPERTIES

Catechol has the chemical formula C6H6O2 and a molecular weight of 110.11 g/mol. Catechol is found as monoclinic crystals or white tablets that discolour in the presence of air and are soluble in water. Although the scent threshold for catechol has not been defined, it has a light, phenolic smell. At 20°C, catechol has a vapour pressure of 0.03 mm Hg. The partition coefficient between octanol and water for it is 0.88 [7, 8].

Catechol is a benzene diol composed of two orthogonal hydroxyl substituents on a benzene core. Catechol is produced on an industrial scale as a precursor to pesticides, perfumes, and pharmaceuticals [9]. It is a common building block in chemical synthesis. Catechol (1, 2-dihydroxybenzene), a typical phenolic pollutant employed in a variety of applications, is present in a number of industrial effluents. It is used as a reagent in the production of rubber and plastic, as well as in the photography, pharmaceutical, and dyeing of fur industries [10, 11]. Catechol (1, 2-dihydroxy benzene) is also extensively utilised to create food additives, hair colours, and antioxidants [12]. Catechols are best recognised for their ease of oxidation because of their high antioxidant activity and low oxidation potentials [13]. The catechol skeleton is one of many naturally occurring substances with anti-inflammatory, antifungal, and antioxidant characteristics [14].

SOURCES, POTENTIAL EXPOSURE AND USES

During production and use, catechol may leak into the environment. Drinking contaminated water and eating contaminated food are the main ways that humans are exposed. Fruits and vegetables naturally contain catechol. Cigarette smoke has been found to contain it [15, 16].

Catechol is used in many different industries, such as photography, fur colour development, antioxidant intermediates in rubber and lubricating oils, polymerization inhibitors, and pharmaceuticals [17]. Skin-to-skin contact is how eczematous dermatitis in humans develops. The condition is identical in humans, although skin absorption produces more severe convulsions than phenol does [18]. Catechol can cause animals' blood pressure to rise for an extended period of time and depress the central nervous system (CNS). The rise in blood pressure appears to be caused by peripheral vasoconstriction [19]. Due to the absence of information regarding exposure duration, it is unclear if these health impacts were observed in the research stated above after acute or chronic exposure. When given orally or topically to rats, mice, guinea pigs, and rabbits, catechol has been demonstrated to exhibit significant acute toxicity [20]. Catechol increased the carcinogenic effects of benzo[a]pyrene on mouse skin when both substances were administered topically [21] Figure 1 consist of structure of catechol and Figure 2 consist of derivatives of catechol.

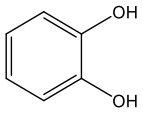

Figure 1: Structure of Catechol (Self created by using ChemBio Draw 14.0 Software)

Derivatives of catechol:

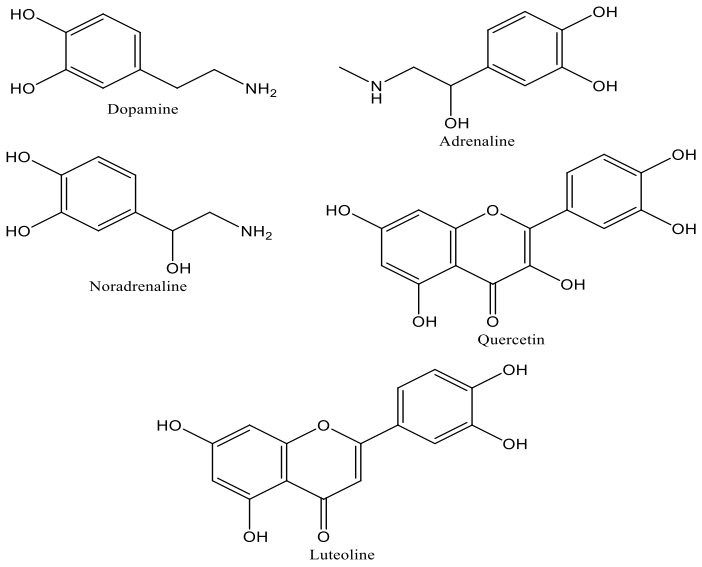

Figure 2: Derivatives of Catechol (Self created by using ChemBio Draw 14.0 Software)

SYNTHETIC METHODS FOR CATECHOL PREPARATION

A semione-pot Pd(II)-catalyzed silanol-directed CH oxygenation of phenols into catechols

A semi-one-pot Pd(II) catalyst during a silanol-directed CH oxygenation of phenols into catechols. This new method functions by going through CH acetoxylation, acid-catalyzed transesterification, and cyclization in that order. Contrary to the known alcohol-7 and phenol-directed cyclization processes, in which the directing group

serves as the oxygen source, our oxygenation technique delivers the oxygen atom of the newly installed hydroxyl group by the oxidant (figure 3). With the aid of this novel method, it is now able to swiftly and precisely build substituted catechols, including electron-deficient catechols that are currently challenging to produce [22, 23].

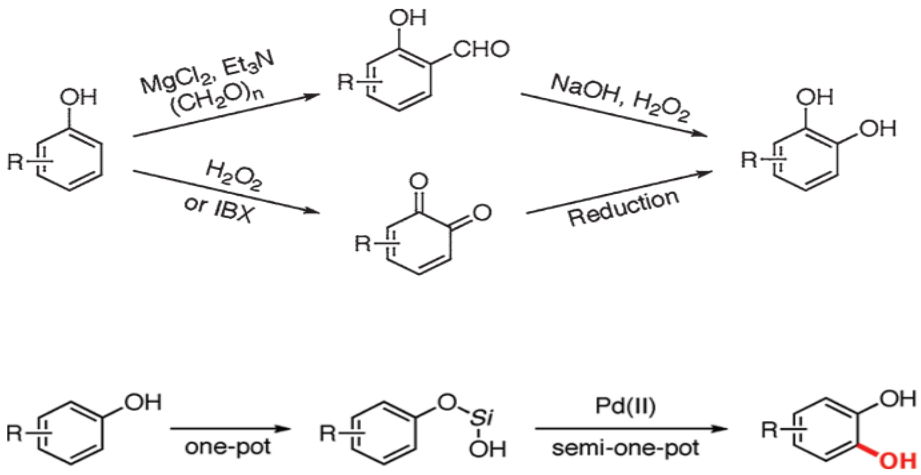

Figure 3: Semi one pot synthesis of cetchol (Adopted from Wicklund, P.A. and Brown, D.G., 1976 and modified by using ChemBio Draw 14.0 Software)

Plausible Reaction Pathway

When $Pd(OAc)_2$ (or palladium pivalate) interacts with silanol 1, the silanol acts as a neutral directing group for the palladium. The result is a palladacycle. 15 After $PhI(OAc)_2$ oxidises PdII in the palladacycle to a higher oxidation state, the intermediate is created (PdIV or PdIII). The 18O-labeling investigations did not produce any product from Pd's direct CO reductive cyclization (vide supra). Instead, a reductive acetoxylation from 9 that regenerates the PdII catalyst produces the observed acetoxylated intermediate (figure 4). Through what is probably an acid-catalyzed transesterification and a subsequent loss of the 18O labelled acetic acid, the latter produces cyclic silyl protected catechol [24, 25].

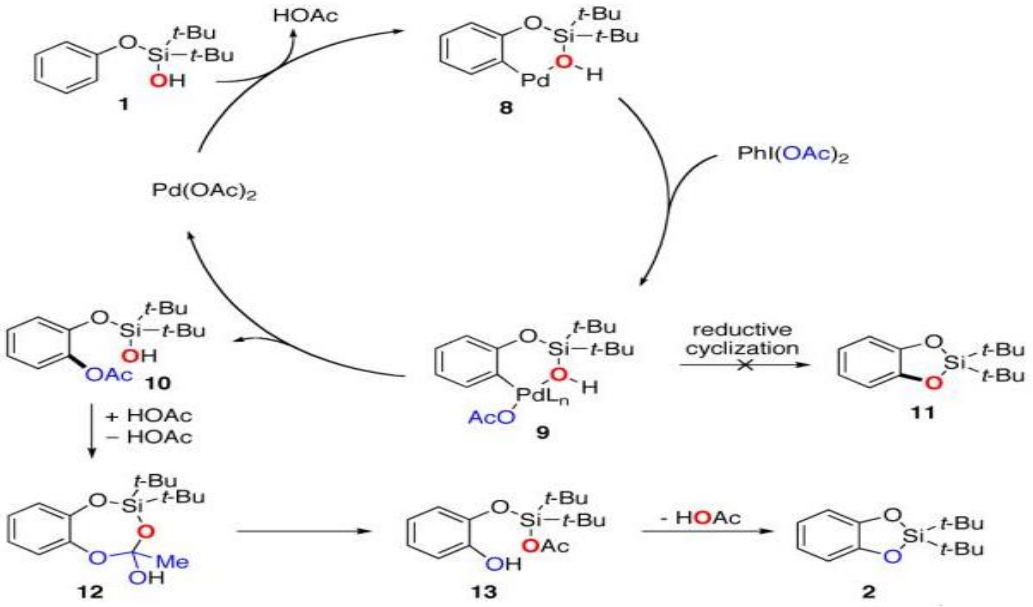

Figure 4: Plausible Reaction Pathway (Adopted from Wicklund, P.A. and Brown, D.G., 1976 and modified by using ChemBio Draw 14.0 Software)

A redox-neutral catechol synthesis

Common tyrosinase catalyses the aerobic oxidation of phenols to catechols by utilising the binuclear copper centres. Here, we report a method for producing catechols that is comparable to the Fischer indole synthesis but is catalysed by iridium, using an oxyacetamide-directed C-H hydroxylation on phenols. The mild, one-step, redox-neutral synthesis of catechols with various substituent groups is possible with this method. Mechanistic studies show that the oxygen supply is provided by the DG oxyacetamide (figure 5). This process has produced a number of important catechols with luminous characteristics and biological activity from the suitable phenols. Finally, our method provides a useful pathway to 18O-labeled catechols by using 18O-labelled acetic acid [26, 27].

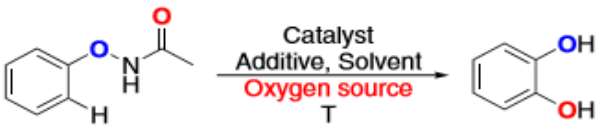

Figure 5: A redox-neutral catechol synthesis (Adopted from Zhao, Y., Song, X., Song, Q. and Yin, Z., 2012 and modified by using ChemBio Draw 14.0 Software)

BIOLOGICAL ACTIVITY OF CATECHOL DERIVATIVES

Antimicrobial activity

Ayyakkannu Purushothaman et al. identified the isolation and characterization of an acyclic isoprenoid from Semecarpus anacardium Linnand its antibacterial potential in vitro. The antibacterial substance that was found in the seeds of the semecarpus anacardium plant has been used to substantiate the plant's usefulness in the treatment of infections. The isolated molecule that was identified as being active in this study may also be useful in the development of brand-new antibacterial drugs. However, more pharmacological, toxicological, and action-mechanics research, which is now being done in our lab, would be needed to support this notion [28].

Zhi Zhou et al. claim that 3D-printed poly(-caprolactone) (PCL) composite scaffolds have antimicrobial activity. Introducing Vancomycin-Doped Polylactic Acid-Glycolic Acid (PLGA) Microspheres. The current work describes the development of a novel composite scaffold for the avoidance and treatment of bone infections. The vancomycin-loaded PLGA microspheres demonstrated good biodegradability in a very short period of time, leading to the local release of the drug at useful quantities. On the other hand, the clinically used vancomycin-loaded PMMA carrier needs to be removed through a second surgery because it does not degrade in vivo [29]. Structure of PLGa as shown in figure 6.

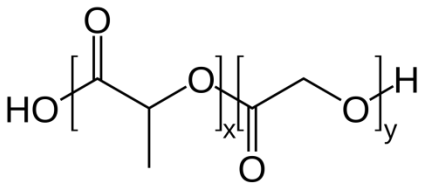

Figure 6: Structure of PLGa (Self created by using ChemBio Draw 14.0 Software)

Zuhura N. Mwangal made the discovery of the Endophytic Fungi Secondary Metabolites from Moringa oleifera (Lam) This study discusses the secondary metabolites extracted from Moringa oleifera endophytic fungus that have antibacterial activity. Fusarium and Nigrospora, two prominent endophytic fungal species that were identified using morphological and molecular methods, are present on the plant. In their secondary metabolites, the isolated endophytic fungi exhibited antibacterial efficacy against the human pathogens Bacillus subtilis, Staphylococcus aureus, and Candida albicans. Furthermore, it was found that the secondary metabolites from crude extracts of endophytic fungal isolates included phytochemicals, indicating that these plants might have therapeutic potential. Further investigation is encouraged to ascertain the toxicity of the secondary metabolites generated by these endophytic fungi in order to pave the way for future therapeutic discoveries [30].

The chemical catechol in Allelo, according to study by Kumari Vishakha et al., entirely shields rice from the bacterial blight brought on by Xanthomonas oryzae pv. oryzae. The major phytopathogen Xanthomonas oryzae pv. oryzae appears to be susceptible to the allelochemical catechol's potential antibacterial and anti-biofilm activities. The anti-biofilm actions of catechol against Xoo were also shown to be caused by its binding to the protein XanA, which produces exopolysaccharides, and its ROS-induced membrane-damaging antibacterial effect. Since catechol has not been shown to reduce the virulence or biofilm of phytopathogenic bacteria To our knowledge, the development of a product to treat Xoo-associated BLB illness will be guided by the findings of this investigation [31].

Anticancer activity

Ji-Yeon Ryu, Hye Rim Kang, and Somi Kim Cho et al. observed changes in phenolic compounds and antioxidant and anticancer activities of blueberries fermented by Lactobacillus plant arum during the course of the fermentation period. In this study, the FBE demonstrated more antioxidant activity than raw blueberry extract. They also shown more efficiency than raw blueberry extract in preventing the proliferation of human cervical cancer HeLa cells while causing very little damage to healthy fibroblast cells [32].

After Marijana Kosani, Branislav Rankovi, and Tatjana Stanojkovi et al. determined that three umbilicaria species exhibit antioxidative, antimicrobial, and anticancer activity, it can be claimed that examined lichen extracts have a strong antioxidant, antimicrobial, and anticancer activity in vitro. According to these results, lichen functions as a healthy and risk-free natural antioxidant, antibacterial, and anticancer agent. It is important to do more study to find novel lichen-derived compounds with potent antioxidant, antibacterial, and anticancer activity [33].

QSAR, Synthesis, and Assessment of Anticancer Activity Study of Caffeic Acid Heterocyclic Esters was found by Farzad Kobarfarda et al. A few caffeic acid heterocyclic esters were made via the Mitsunobu process. Other methods of esterification may have failed to produce the necessary molecules because of the sensitive nature of the catechol ring in the structure of cafeic acid. The esters were further modified by adding benzensulfonyl or toluene-4-sulfonyl groups to their catechol rings using the cyclic voltammeter method. An assessment of the compounds' cytotoxic activity showed that they are more effective against the HeLa cancer cell line when compared to SK-OV-3 and HT-29. According to QSAR studies, these compounds' molecular structure primarily affects how lethal they are. When present, arylsulfonyl groups decrease activity, maybe as a result of the electron withdrawing and/or steric influence [34]. Structure of caffeic acid phenethyl ester as shown in figure 7.

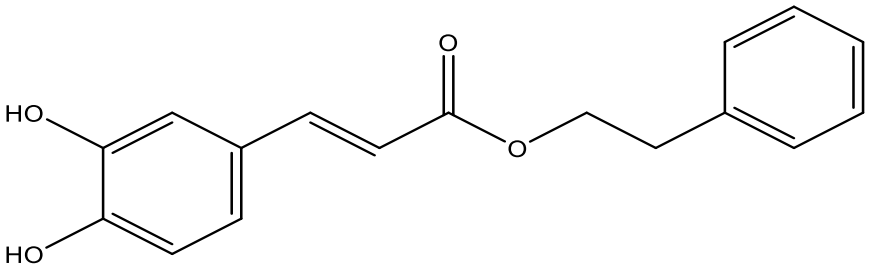

Figure 7: Structure of caffeic acid phenethyl ester **(Self created by using ChemBio Draw 14.0 Software)**

According to in vivo research by H. P. Vasantha Rupasinghe et al., cranberry proanthocyanidins (figure 8) are biotransformed into probiotic metabolites by Lactobacillus rhamnosus, which boosts their anticancer action in HepG2 cells. Despite the rapidly growing body of research on fruit polyphenols and their potential health benefits, the limited bioavailability of polymeric proanthocyanidins encourages the development of biotransformation techniques [35].

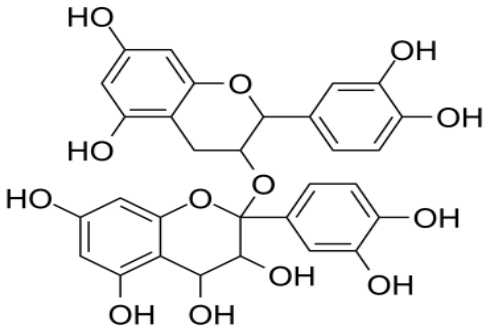

Figure 8: Structure of proanthocyanidins (Self created by using ChemBio Draw 14.0 Software)

Antiviral activity

According to research by Takashi Watanabe and colleagues, the pyroligneous acid's catechol derivatives show structure-dependent antiviral effect against the encephalomycarditis virus. Strong antiviral activity was shown by the pyrolyzed WV from Japanese larch against EMCV. Catechol and its derivatives with various substituent

groups served as the main antiviral agents in the WV. Depending on how the function groups were arranged and structured in relation to an aromatic skeleton, these components displayed varying levels of antiviral activity. It was discovered that the catechol derivatives instantly render EMCV inactive, produce ROS, and increase cytokine Il6 production. These results will pave the way for the creation of highly effective catechol-based antiviral drugs as well as a method for creating antiviral chemicals from lignocellulosic biomass [36, 37].

By testing the antiviral activity of PAs from hardwood, softwood, and bamboo against EMCV, Ruibo Li, Ryo Narita, et al. discovered that phenolic compounds in pyroligneous acid from Hardwood, Softwood, and Bamboo had against viruses. Every PA exhibited potent antiviral activity, with the exception of Japanese red pine wood. The PAs contained 25 different phenolic derivative types, which were identified and measured. All phenolic compounds were tested for their antiviral efficacy against the EMCV, and it was discovered that the functional groups attached to the aromatic ring and their relative locations have a substantial impact on the antiviral activity. Catechol and its derivatives have been shown to have stronger antiviral action. Comparatively speaking, phenolic compounds with methyl groups exhibited stronger antiviral activity than those with methoxyl groups. These findings offer a novel method for determining the concentration of each phenol derivative from various plant sources, maximising the manufacture of antiviral drugs from PAs. The creation of more potent medications for the treatment of virus inactivation can benefit from an understanding of the relationship between phenol derivative structure and action. Utilizing PAs as a source of antiviral phenolic compounds for the treatment of viral infections is a particularly alluring and environmentally friendly strategy due to the abundance and renewability of waste biomass [38, 39].

According to a study by Jeffrey Langlanda et al., the antiviral medicines rosmarinic acid, chicoric acid, and chlorogenic acid are effective against the herpes simplex, VSV-Ebola pseudotyped, and vaccinia viruses. The main finding of this research was that the presence of iron(III) ions can significantly boost the anti-HSV action of compounds with caffeoyl functional groups. Unlike the intracellular mechanism of acyclovir, the mechanism of action appears to be a suppression of virion attachment to the cells. This shows that the usage of acyclovir and the chelates of caffeic acid may be employed to boost viral control without encountering the toxicity problems connected with only raising the dosage of acyclovir. Last but not least, the chelates have extremely low toxicity to cells due to their widespread and benign character, and it is anticipated that this toxicity will also apply to organisms. Future studies should combine acyclovir with caffeic acid chelates to ascertain whether the effects are additive. A detailed mechanism of action analysis is also needed to fully understand how the caffeic acid chelates work. The efficacy and pharmacokinetic characteristics of the caffeic acid chelates must be examined in animal models [40, 41]. Structure of catechol based derivatives with EC_{50} Value as shown in figure 9.

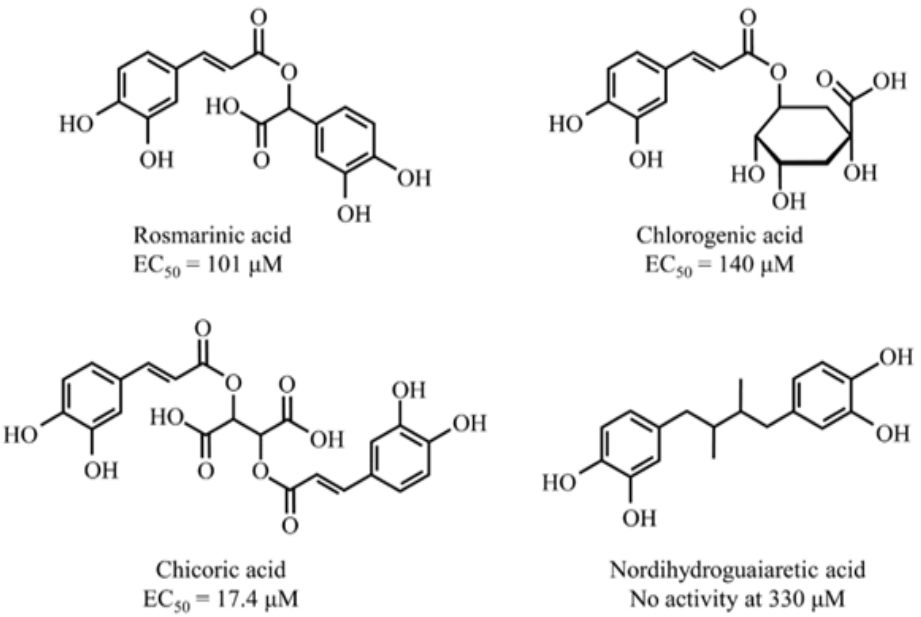

Figure 9: Structure of catechol based derivatives with EC_{50} Value (Adopted from De Pinedo, A.T., et al., 2005 and modified by using ChemBio Draw 14.0 Software)

According to Rubén Solórzano et al., versatile iron catechol-based nanoscale coordination polymers with antiviral ligand functionalization and their use as efficient carriers in HIV/AIDS therapy. We have developed and produced novel iron-catechol-based nanoscale coordination polymers that contain a prodrug molecule

attached to a catechol ligand. To show the potential of this nanoplatform, we used a catechol ligand (catAZT) connected to the well-known antiretroviral AZT by an enzymatically cleavable ester bond. Coordination polymer nanoparticles with an average size of 147 5 nm allowed for the constant incorporation of catAZT with large payloads [42, 43]. The effective antiretroviral activity of free AZT prodrug was successfully replicated using this approach, and nano structuring offers the following notable advantages: (I) stabilisation of the drug in physiological media as a colloidal suspension; (II) control over the release properties of the drug by pH and the presence of enzymes; (III) the nanoparticles retain inherent multifunctionality due to the presence of iron ions with MRI responses; and (IV) significati (up to 50-fold increase). CatAZT -NCPs demonstrated good anti-HIV efficacy in cell studies at levels comparable to free AZT but over longer durations. According to earlier research, tethering active drugs to coordinating ligands is a novel but promising class of carriers that can optimise the pharmacological characteristics of well-known antiretrovirals with controlled release while drastically reducing side effects brought on by systemic toxicity effects. Studies are currently being undertaken to see if this novel approach may be used for other disorders that present similar issues. The capacity of this new class of nanocarriers to address drug transport difficulties, improve bioavailability in tissue sanctuaries and latently infected cells, and improve cellular absorption is anticipated to help the future generation of pharmacological approaches for HIV treatment [44, 45].

The capability of carnosic acid to resist the respiratory syncytial virus was identified by Han-Bo Shin and associates. There is an urgent need for novel therapies due to the toxicity of ribavirin and its lack of effectiveness in treating hRSV infection. Carnosic acid prevents hRSV infection and reproduction, as seen in Figure 8. (A) Carnosic acid was injected into A549 cells both before and after the virus was put into them at various intervals. Inhibitory effects were investigated by tracking the creation of the viral F and NS2 proteins in RNA. (B) Cells were exposed to carnosic acid for an entire hour. For one hour, cells were exposed to hRSV A2 as follows: Carnosic acid was removed from cells by washing them five times in PBS. Car++, cells that had previously been cultured in medium containing carnosic acid before being infected with a hRSV inoculum that included the acid. hRSV-infected cells lacking carnosic acid are referred to as car-. Car+, carnosic acid-containing hRSV inoculum-infected cells. The present work demonstrates that carnosic acid, a dietary preservative and antioxidant, effectively inhibits hRSV replication. Carnosic acid not only reduced viral RNA synthesis but also stopped hRSV from infecting cells in the first place. As a result, carnosic acid therapy greatly reduced the generation of hRSV progeny viruses. Given that therapy with carnosic acid both pre- and post-exposure decreased hRSV replication, it may be a feasible preventative and therapeutic medication against hRSV infection [46, 47].

Antioxidant activity

By Angels González-Lafont et al., "Tunnelling in Green Tea: Understanding the Antioxidant Activity of Catechol-Containing Compounds." Variational Transition-State Theory: A Study The various polyphenolic substances present in green tea, especially catechins, are widely acknowledged to have anti-cancer, anti-inflammatory, and anti-cardiovascular properties. In biological issues and subcellular fractions, catechins dramatically reduce lipid peroxidation, which has been connected to their antioxidant activity by scavenging free radicals as the main driver of these protective advantages. The capacity of catechins to act as antioxidants appears to be largely attributed to the dihydroxy functionality of the catechol molecule.

Lurdes Mira et al. claim that a catechol derived from abietic acid has antioxidant activity.

However, MDTO is less effective than quercetin in the DPPH experiment. MDTO's antioxidant activity is comparable to that of kaempferol and taxifolin, two additional flavonoids with recognised antioxidant activity. The MDTO also scavenges the ABTS radical cation. In accordance with the energetics of the O-H bonds in these compounds as well as many structural features of the two molecules, quercetin has a higher free radical reactivity than MDTO. MDTO also scavenges hypochlorous acid and inhibits lipid peroxidation. The interactions between flavonoids and membranes, which point to an increase in quercetin content at the lipid-water interface of membranes, can be used to explain MDTO's lower membrane antiperoxidative efficacy. We believe that the results for MDTO are trustworthy primary indicators for evaluating the antioxidant activity of the drug in vivo, despite the fact that they were acquired in vitro using less sophisticated systems [48].

Catechol-containing block copolymer micelles, according to Urara Hasegawa et al. Structure characterization and antioxidant activity We produced a block copolymer consisting of a PAM block and a carboxyl group-containing poly (N-acryloyl glycine) block using the RAFT polymerization method. This polymer was grafted with DA via DCC/NHS coupling to create amphiphilic PAM-PDA block copolymers. DLS, AFM, and LALS were used to show that stable micelle structures formed at grafting degrees of about 60% and higher. This difference in polymer structure significantly affected the properties and function of catechol moieties in terms of oxidation stability, H2O2-scavenging activity, and inhibitory effects on the formation of endothelial cell tubes. The other micelles were stable for 10 days, but PAM-PDA18 quickly oxidised in air, according to UVeVis

examination. According to cyclic voltammetry studies of the different polymers, the stated redox potentials had no effect on the electrochemical reactivity of catechol groups, but the micelles had a noticeable retardation impact on the electrochemical process. Additionally, the micelles scavenged less H2O2 in comparison to DA. We therefore propose that the O2 and H2O2 mass transfer constraints into the micellar core are responsible for the decreased H2O2-scavenging activity and increased oxidation stability of the micelles. The micelles' greater oxidation stability than DA was demonstrated to be essential for exerting an anti-angiogenic impact in the HUVEC tube formation experiment [49].

Luisa Maria Migneco et al. identified the antimicrobial activity of catechol functionalized-chitosan against Staphylococcus epidermidis. The primary objective of this work was to investigate the antibacterial capabilities of catecholfunctionalized chitosan for potential application as a wound dressing. Chitosan, which was largely utilised for this purpose, was functionalized with hydrocaffeic acid, which has a catechol group, by carbodiimide-mediated condensation. A simple and efficient method was used to preserve the catechol moiety of hydrocaffeic acid. The best systems in terms of combination antibacterial and antioxidant effect were found to be CS-HCAF derivatives. In particular, CS-HCAF20 displayed a MIC that was four times lower and an EC50 that was 700 times lower than CS. The antibacterial activity of CS-greater HCAF20 decreased S. epidermidis adhesion to commercial dressings in comparison to CS. Overall, these findings suggest that catechol moieties may enhance the muco-adhesiveness, antioxidant, and antibacterial activity of chitosan, all of which are essential for application in wound healing [50].

According to M. Begon a Ruiz-Larrea et al., catechol and phenol oestrogens have different anti-oxidant effects on aqueous and lipophilic radicals. The elimination of free radicals generated in both the aqueous and lipophilic phases is significantly aided by oestrogens. The extent and effectiveness of their protective effects varies depending on whether the molecule has a phenolic or catecholamic structure. The exact inhibitory mechanism in the LDL system, which has several components that collectively contribute to the overall antioxidant impact, is determined by the mono- or dihydroxy-group connected to the aromatic A ring. The fact that human oestrogens do not interact with a-tocopherol in LDL is an important discovery, but the full biological significance of these in vitro and ex vivo studies on natural oestrogens is still not entirely understood [51].

Antineoplastic activity

Pyrrolobenzodiazepines (PBDs) are exceptional sequence-selective DNA alkylating agents with anti-tumor activity, according to Barbara Gerratana et al. They were found to have bioactivity. Actinomycetes either produce them synthetically or spontaneously. A variety of PBDs, including dimeric and hybrid PBDs, were synthesised as a result of the astonishingly diverse range of functions of naturally occurring PBDs, which increased this class of molecules' potency and DNA-binding sequence specificity [52].

Mushrooms may function as antibacterial and antioxidant agents, per Marijana Kosani et al. It can be said that researched mushroom extracts show strong antioxidant and antibacterial effects in vitro. On the basis of these findings, mushrooms appear to be safe and beneficial natural sources of antioxidants and may play a significant role in human therapy, the treatment of animal and plant illnesses, and food preservation. Further research should be done on the isolation and characterization of new compounds from mushrooms that have antibacterial and antioxidant activities [53].

CONCLUSION

Due to the wide range of biological and therapeutic applications for both naturally occurring and manufactured catechol, researchers are looking into the production processes of this class of compounds and assessing their pharmacological activity. In this review, catechol has been highlighted as a unique scaffold in medicinal chemistry. The pharmacological action of these compounds varies depending on the pattern of substitution on the catechol moiety; the review mainly focuses on catechol synthesis methods and catechol derivatives. The majority of study has been on the derivatization of the entire catechol molecule, even though catechol showed promise in a number of biological activities, including anticancer, antioxidant, anti-inflammatory, antibacterial, and anti-diabetic. Various coumarin synthesis methods are covered in the sections that follow. However, these molecules lack the biological activity that, in our opinion, could lead to a number of new therapeutic possibilities. It should be emphasized that a number of biologically active and potent molecules have been characterized with diverse substitutions. This review may inspire the usage of catechol scaffolds and further functionalizations to develop novel structural motifs in medicinal chemistry and drug discovery.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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