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Review

Crosslinking Mechanisms of Phenol, Catechol, and Gallol for Synthetic Polyphenols: A Comparative Review

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Abstract: Since the first introduction of a synthetic polyphenol called polydopamine, both it and its derivatives have received significant attention from material scientists owing to their unique functionality. In particular, synthetic polyphenols have been utilized as interfacial engineering tools; many important review papers have been published regarding this topic. However, despite those that have focused on the applicability of synthetic polyphenols, fundamental aspects of crosslinking mechanisms and resultant characteristics have still been overlooked in the community. This review covers the mechanisms for building synthetic polyphenols, which are dependent on the number of hydroxyl groups of each phenolic building block. The inherent physicochemical properties of the developed polyphenolic materials are discussed in depth herein. This review can provide guidelines for selecting appropriate phenolic building blocks when designing relevant polyphenolic biomaterials.

Keywords: synthetic polyphenols; biomaterials; biomimetics; phenolic building block

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1. Introduction

Optimized mechanisms within living organisms often provide invaluable inspiration when designing functional materials from a chemical point of view. Among these, polyphenols have received significant scientific attention owing to their diverse physiological roles in nature [1–3]. A well-known characteristic of natural polyphenols—commonly found in mussel-foot proteins with a high content of 3,4-dihydroxyphenyl-L-alanine (DOPA), a phenolic amino acid, is their underwater adhesive ability [4]. The wet adhesiveness of the mussel-foot protein is attributed to the catechol side chain of DOPA. Catechol can maintain adhesion through various non-covalent and covalent bonds at the interface, in addition to generating a strong cohesive force due to oxidative self-crosslinking [5]. Additionally, polyphenols play an essential role in the hardening of the insect exoskeleton (i.e., cuticle) to protect them from external attacks [6]. Specifically, the curing process begins with the action of oxidases—such as phenoloxidase—on phenolic precursors such as N-acetyldopamine and N-β-alanyldopamine [7]. Another polyphenolic material, i.e., melanin, is a major component of the ink used by cephalopods to block the vision of predators. The oxidative polymerization of the L-DOPA results in the formation of 5,6-dihydroxyindole-2-carboxylic acid (DHICA), which is an intermediate that is involved in the formation of melanin [8]. In short, natural polyphenols with diverse physiological roles can be developed by oxidative crosslinking mechanisms.

Inspired by the mechanism, synthetic polyphenols developed from phenolic building blocks have been introduced. Polydopamine [9–13], poly(L-DOPA) [14], poly(norepinephrine) [15–17], poly(gallic acid) [18], and poly(tannic acid) [19–21] are typical examples; the materials showing similar physicochemical properties to the natural polyphenols have been successfully used as adhesives, optical materials, sensors, and other bioinspired applications [12–14]. Especially due to their excellent biocompatibility [22,23], biodegradability [24], and wet-adhesion abilities [25,26], the self-assembled phenolic building blocks

have been successfully utilized as biomaterials, such as nanomedicine, antimicrobial coating, and tissue scaffold (Figure 1).

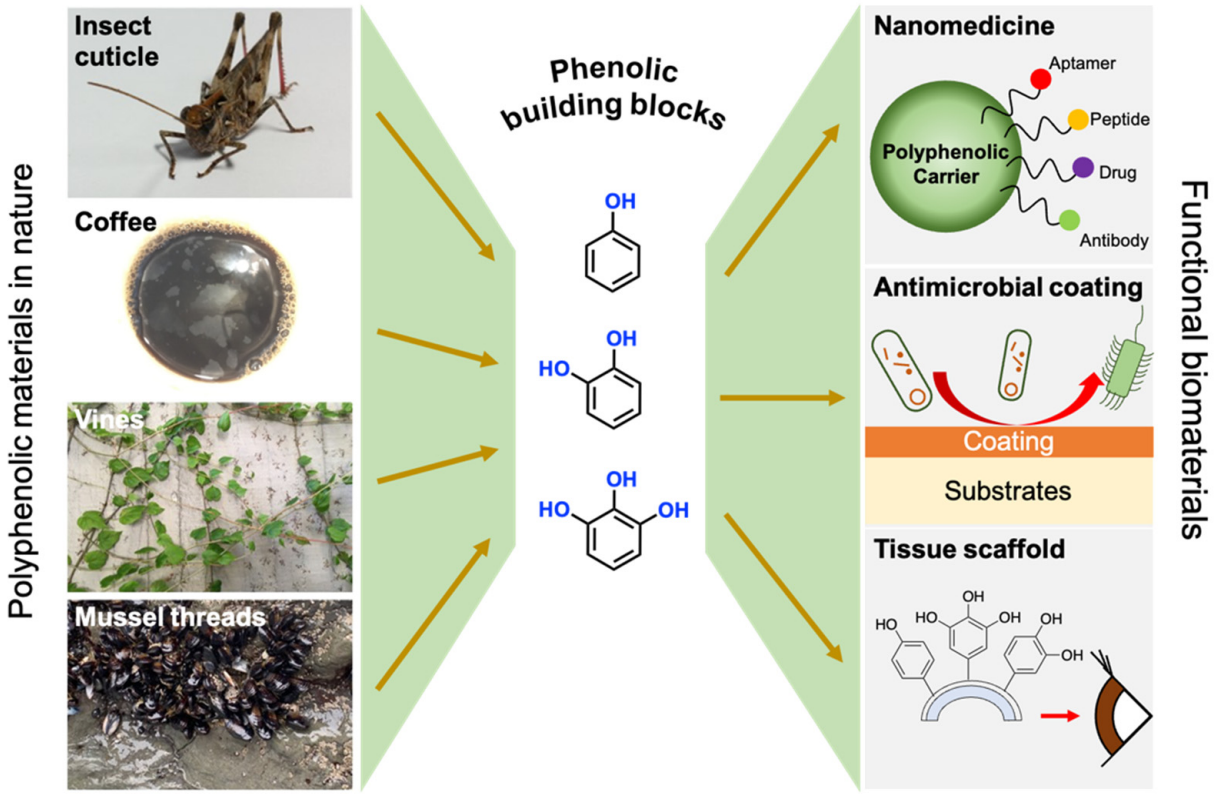

Figure 1. Bioinspired approach for developing functional biomaterials by using phenolic building blocks.

While their usability was confirmed in previous studies, the detailed assembly mechanisms of individual phenolic building blocks have been overlooked in the community. In fact, each phenolic building block has a different number of hydroxyl groups in the benzoic site. The structural dissimilarities influence the chemical interactions that integrate into the building blocks. For example, quinone, which is the critical intermediate that can initiate the oxidative chain reaction [27], can be developed in catechols and gallols but not in phenols. Thus, the oxidative crosslinking kinetics is relatively slow when an aromatic compound with a single hydroxyl group (i.e., phenol) is used; enzymes, oxidants, and other catalysts are often required to induce the associated polyphenols [28]. On the other hand, oxidation can be spontaneously achieved in catecholic molecules in the presence of ambient oxygen. If there is an additional hydroxyl group in the catechol group (i.e., gallol), the oxidative crosslinking reaction can be further facilitated [29,30]. The difference in assembly kinetics significantly impacts their physicochemical properties. Thus, placing an appropriate polyphenol in a suitable application is essential.

In this review, we classified representative building blocks that can develop synthetic polyphenols into three categories based on the number of hydroxyl groups (i.e., phenol, catechol, gallol, see Figure 2). Additionally, the relevant self-assembly mechanisms and resulting biomaterials have been described. The information presented in this review will be beneficial when designing a new polyphenol-based functional biomaterial.

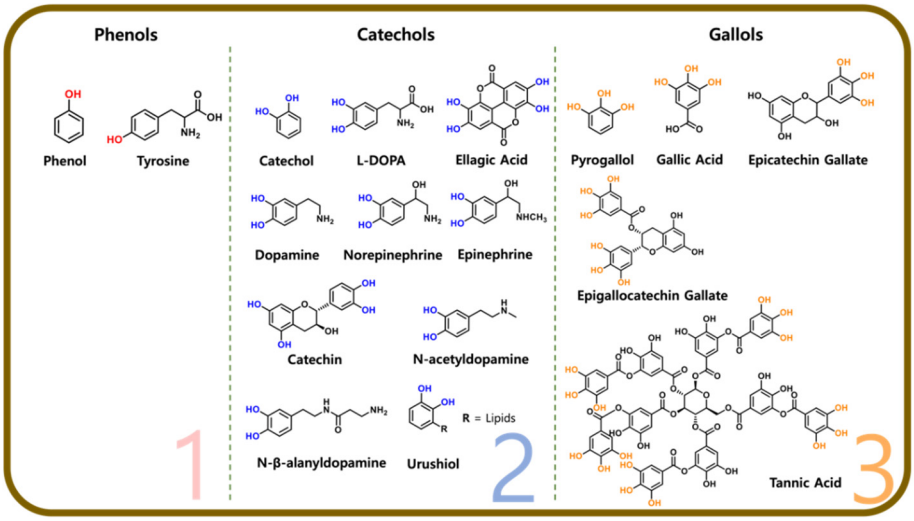

Figure 2. Classification of phenolic building blocks that can be used for developing synthetic polyphenols. The numbers indicate the number of hydroxyl group in each phenolic molecule.

2. Hydroxybenzene-Based Building Blocks (Phenol)

The simplest building blocks that contribute to the development of synthetic polyphenols are hydroxybenzene-based (phenolic) molecules that have one hydroxyl group in their benzoic residue. Tyrosine is the representative phenolic molecule. In general, the phenolic group in tyrosine plays an important role in stabilizing the assembled polyphenolic structures by inducing the formation of non-covalent bonds (e.g., hydrogen bonds and π–bonds) [31] and biphenol bridges, resulting in dityrosine formation [32] (Figure 3). Dityrosine formation can specifically contribute to increasing the elasticity and structural solidity of synthetic polyphenols while also reducing the fatigue of self-assembled materials [33]. For example, resilin, an insect-derived elastic protein found in the wings of dragonflies and the legs of cockroaches, contains dityrosine or trityrosine, thereby enabling their fast movement [34,35]. Studies have been performed to mimic the aforementioned systems to reinforce the mechanical properties of artificial functional materials. For instance, redox enzymes [36,37], Fenton reactions using hydrogen peroxide and iron ions [38], and ruthenium-based photoinitiators [39] have been used to induce the formation of biphenol crosslinking, which contributes to nanoscale or larger-scale assembly processes and increases the structural stability of synthetic polyphenols.

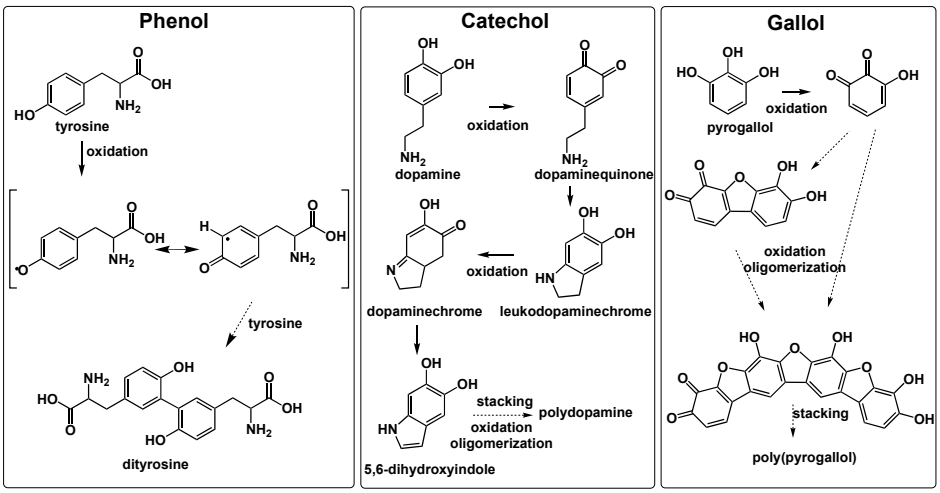

Figure 3. Representative self-assembly mechanisms of phenolic building blocks: phenol vs. catechol vs. gallol.

3. Dihydroxybenzene-Based Building Blocks (Catechol)

The self-assembly mechanism of dihydroxybenzene (catechol)-based phenolic building blocks has been actively studied in the past few years. Quinone is first formed from catechol, after which the electrophilic quinone can be reactively conjugated with a nucleophile (e.g., amine or thiol) through Michael-type addition or Schiff base formation [5]. As a result, catecholamine-based building blocks (e.g., dopamine, norepinephrine) generally form dihydroxyindole (DHI) intermediates that strongly facilitate self-assembly [14,40]. This paper examines the detailed self-assembly mechanisms of these molecules for developing synthetic polyphenol-based biomaterials.

3.1. Dopamine

Polydopamine was introduced in 2007 and is the first reported synthetic polyphenol-based material [4]. Dopamine is a basic building block that has both catechol and amine groups in its molecular structure and exhibits a self-assembly mechanism similar to that of eumelanin [14,41]. The oxidation of dopamine results in the production of DHI through a quinone structure (Figure 3). DHI formation mainly contributes to the production of self-assembled polydopamine in two ways, (1) assembly with additional covalent bonds (e.g., DHI–DHI dimer formation) and (2) assembly with non-covalent bonds [42]. In addition to DHI, other intermediates can also be involved in the self-assembly mechanism; however, the complete polydopamine structure has not yet been fully elucidated due to its complexity.

Polydopamine has been widely adopted for biomaterials, as it can provide catechol functionality to virtually any kind of target substrate upon employing the simple dip-coating process [43,44]. Moreover, polydopamine has a high potential to contribute to cellular responses. Thus, it has been utilized as a novel tissue scaffold coating material that brings successful transplants. For example, polydopamine can stimulate osteogenic cell differentiation, which consequently promotes osseointegration [45]. This process can be achieved due to the enhanced hydrophilicity of the scaffold materials via polyphenol coatings, which increase the adsorption of biomacromolecules from the extracellular matrix, thereby enhancing cell adhesion, proliferation, and differentiation; recently, in vivo studies on polydopamine-assisted bone regeneration have been actively conducted [46–49]. Moreover, polydopamine can be beneficial for extending the blood circulation time of benzoic drugs. Here, π–π stacking plays a crucial role in chemically stabilizing drug agents. For example, two antitumor drugs (gossypol and doxorubicin) are highly stabilized by a polydopamine-based nanocarrier, which can significantly extend blood circulation time with two orders of magnitude difference compared to that of free gossypol and/or doxorubicin [50].

3.2. Dopamine Derivatives

Neurotransmitters derived from dopamine can also be self-assembled into polyphenols; for example, norepinephrine can be assembled into poly-norepinephrine [51]. Norepinephrine shares a molecular structure similar to that of dopamine and can also form DHI or its analogs to greatly contribute to the oxidative polymerization process [51]. When quinone (i.e., the oxidized form of catechol) is formed, 3,4-dihydroxybenzaldehyde (DHBA) is also formed by tautomerization; thus, the DHBA intermediate can be spontaneously formed [16]. This intermediate has an extra hydroxyl group compared to DHI and has been reported to play a vital role in reducing the roughness of coated polyphenols [16]. When the nucleophilic amine group is protected by a methyl group (i.e., epinephrine), the homogeneity of synthetic polyphenols can be further improved [52]. The aforementioned results indicate that the physicochemical properties of the developed synthetic polyphenols can be fine-tuned by corresponding to the molecular structure of the building blocks, which requires further research.

3.3. Catechin

Catechin is a representative flavonoid that is found in plants and has been overlooked during functional polyphenolic coating as a potential building block. In general, there are two methods to form polyphenols by self-assembling catechins in aqueous conditions. The first involves utilizing sodium salts that enhance the cation–π interaction [53], while the other involves generating radicals from catechins by irradiating with UV light for polymerization [54]. There are significant differences in the assembly mechanisms between these two methods. In general, catechol-based phenolic components (especially catecholamines) are more likely to self-polymerize under weak alkaline conditions. However, the mass spectrometry data corresponding to the poly-catechin formed in a saline buffer with a slightly basic pH [55] demonstrated that physically stacked catechins were the majority instead of covalently conjugated catechins such as dimers (or trimers). This indicates that catechin cannot be solely crosslinked under basic conditions, which is a phenomenon that may be attributed to the relatively high pKa values of catechins [56], which induce hydroxyl group protonation to inhibit quinone formation in the catechol groups. According to an existing study, the successful poly-catechin formation can be achieved by inducing the formation of non-covalent cation–π interactions between the catechin and sodium ions [57]. As the polyphenolic layer is non-covalently crosslinked, the mechanical stability of the poly-catechin is assumed to be weak. Unfortunately, no fundamental studies on the mechanical stability of the catechin coating have yet been performed. UV irradiation is another technique that can be used for developing self-assembled catechin. Unlike sodium-mediated non-covalent self-assembly, UV irradiation-induced self-assembly involves the generation of free radicals in the molecular structure to trigger covalent cross-linking [54]. After UV irradiation, a strong signal in the higher wavelength region was observed in the UV-vis spectrum due to pigmentation, which is strong evidence of catechin polymerization.

Catechin-derived polyphenols have been adopted as therapeutic carriers (e.g., drug delivery systems) since they have the advantage of grafting medical agents. In detail, the chemical conjugation between catechols in poly-catechin and nucleophilic functional groups in therapeutic agents can be achieved by a simple one-step functionalization process similar to other catechol-based polyphenols. However, the issue of this approach relies on the irreversible binding between the polyphenolic carriers and therapeutic agents, which may reduce or even inactivate their biological activity. Numerous studies have been performed to solve the problem; grafting target biomolecules to polyphenols through reversible dynamic bonding (catechol–boronic acid interactions) is a typical breakthrough strategy [58]. As the developed system showed minimal cytotoxicity, and the therapeutic agents can be released intact, the bioactivities can be successfully conserved. Similarly, a boronate proteasome inhibitor (bortezomib) encapsulated by a poly-catechin-based nanocarrier was developed, which allowed the controlled release of undamaged bortezomib at the targeted cancer site [59].

3.4. Alkylcatechols

Alkylcatechols, such as urushiol and its analogs, are found in lacquer trees. These are amphiphilic molecules that consist of two parts: a relatively hydrophilic head (i.e., catechol) and a hydrophobic tail (i.e., alkyl chain) [60], which can be assembled into polyphenolic materials. Assembled polyphenols have been adopted as protective coating materials for furniture and industrial equipment owing to their strong shear strength, as well as their chemical resistance to heat and moisture [61]. The advantage of alkylcatechols is that they can be prepared as an emulsion due to their amphiphilicity, which allows the lacquer to be extremely concentrated in low amounts of water. Concentrated catecholic extracts allow direct surface coating with simple painting because of their sticky nature. Subsequently, oxidative polymerization between urushiol and its analogs continues, resulting in a stable polyphenolic layer similar to that produced through the self-assembly mechanisms of the previously described catecholic building blocks. An important aspect to note is that an oxygen source that involves oxidative polymerization is mainly provided from the ambient

air in alkylcatechol-based extraction rather than the solution. Moreover, the quinone formation that promotes polyphenol development can be accelerated by a naturally occurring oxidase (e.g., laccase) that exists in the lacquer tree [62]. Catechol–metal complexation or additional crosslinking reactions at high temperatures could also promote and stabilize the self-assembly of urushiol [63]. Moreover, the oxidative crosslinking of urushiol can also be activated through UV-induced photocuring, similar to the mechanism underlying catechin assembly [64].

4. 1,2,3-Trihydroxybenzene (Gallol)

Gallic molecules also act as phenolic building blocks in oxidative polymerization when developing synthetic polyphenols. Naturally occurring gallol-based molecules include pyrogallol, gallic acid, catechin derivatives (e.g., epigallocatechin gallate), and tannic acid, all of which are found in various organisms, including plants. Gallic polyphenols share a molecular backbone with catecholic polyphenols, thus exhibiting similar characteristics. For example, gallol-based polyphenols are involved in enhancing the mechanical properties of plant cell walls [65] and act as antimicrobial agents [66]. A distinctive characteristic of gallol-based building blocks is that their self-assembly proceeds very quickly compared to that of catechols owing to the presence of additional hydroxyl groups. Moreover, the chemical interactions with neighboring substrates can be relatively reversible owing to the high potential of forming non-covalent bonds (e.g., hydrogen bonds) and metal–ligand complexation. This highlights another feature of gallol-based polyphenols, i.e., self-healing; the utilization of this mechanism by tunicates to self-heal internal damage is well known [67,68]. We will discuss the formation of representative gallol-based polyphenols in further detail in the following sections.

4.1. Pyrogallol and Gallic Acid

Pyrogallol is the simplest form of a gallol-based building block; gallic acid is a representative derivative of the same [18]. Both molecules are abundant in plants, and they can be easily produced by extracting natural products or biosynthesis using microbial organisms [69]. These molecules are thus highly accessible and can be successfully utilized for the synthesis of polyphenol materials on a large scale. The self-assembly mechanism of gallol-based building blocks is more complicated than that of catechol-based ones, which serve as a bottleneck during the application of gallol-based polyphenols. Similar to catechols, gallols also have the potential to produce quinone derivatives during the oxidation process (Figure 3). As a result, a variety of crosslinks, such as galloquinone dimers that are further transformed into purpurogallin, can be generated [29]. Oxidizing agents such as $NaIO_4$ can accelerate this crosslinking process [30]. UV irradiation is another trigger that facilitates crosslinking [70]. If additional nucleophilic molecules or metal ions are present, the crosslinking can be further accelerated owing to the formation of covalent bonds between the nucleophilic functional groups (e.g., -NH_2, -SH) and the electrophilic quinone [29,71] and metal coordination between the gallol and a metal ion [72]. The aforementioned crosslinking mechanisms are comparable to those of catechol. One critical difference in the polymerization process is that crosslinking can be achieved very quickly in gallol-based building blocks, but the process takes longer for catechol. For example, the free-standing film formation of pyrogallol at the water/air interface via oxidative polymerization in an amine-rich polymer solution can be achieved in 2 min, which, in the case of pyrocatechol, is 2 h [29,73]. This difference shows the effect of an additional hydroxyl group (-OH) on the kinetics of cross-linking.

4.2. Tannic Acid

Tannic acid is another gallol-based building block that is found in plants. The physiological roles of tannic acid include antimicrobial and antioxidant properties [74]. These abilities are maintained even when tannic acid is polymerized to form polyphenols. For example, the antibacterial ability of tannic acid can be successfully transferred to the poly-

tannic acid-deposited substrate [19]. In this regard, tannic-acid-containing spray-based coating techniques were introduced [75,76], which enabled rapid polyphenol coating on the bulk substrates. However, it is difficult to completely prevent the adhesion of bacteria to the modified polyphenol surface, and the inherent antimicrobial ability of tannic acid can be easily inactivated and blocked by the formation of an additional layer composed of killed bacteria [77]. The insertion of supplementary antibiotics and antifouling agents in polyphenol coatings can ameliorate this problem. For example, antimicrobial peptides deposited with poly-tannic acid showed both resistance and killing effects on the bacteria [78].

The difference between tannic acid and other phenolic building blocks is that tannic acid has a relatively high molecular weight. Due to this, the Van der Waals forces in tannic acid are relatively stronger than those in other phenolic molecules; this enables the stable physical stacking of tannic acid, while the occurrence of covalent crosslinking is relatively low. Thus, tannic acid-based synthetic polyphenols are comparatively colorless compared to other polyphenol-based materials such as polydopamine. Poly-tannic acid can thus be a substitute for other polyphenolic coating materials where the substrates require transparency (e.g., contact lenses and dental implants). In addition, tannic acid-based nanocarriers allow targeted therapeutic delivery to the heart, which is one of the most difficult target sites due to the dynamic movement of body fluids [79]; it is possible since the tannic acid shows a strong binding affinity to the myocardium of cardiac tissue [79].

5. Conclusions and Discussion

As discussed previously, polyphenols developed through the self-assembly of phenolic building blocks have the potential for use in numerous biomedical applications. Specifically, it is encouraging that their applications can be further expanded through nanotechnology. However, there are different kinds of biocompatibility issues in nanoscale biomaterials compared to those of bulk scale. For example, polyphenol nanoparticles injected for therapeutic purposes circulate through the blood vessels, which can lead to unexpected accumulation or side reactions with adjacent biomacromolecules. Some studies have recently suggested the possibility that quinones, i.e., derivatives of catechol groups and other intermediates, may act as an allergen site as they generate antigens by forming covalent bonds between membrane proteins. Urushiol is known as a potent allergen that causes skin allergic reactions. Polyphenols and related building blocks may interfere with the physiological systems that employ chemically resembled small molecules such as neurotransmitters (i.e., dopamine, epinephrine, and norepinephrine). In this respect, few studies have been conducted to investigate the cytotoxicity of polyphenol nanoparticles. To address this, both immunological and metabolic studies on polyphenolic materials should be performed. In addition, despite active research on synthetic polyphenols for the past several decades, their exact molecular structures have not yet been elucidated clearly. The uncertainty of the molecular structure is the main reason for the rejection of clinical approval. Thus, a new approach to interpreting the complex self-assembly mechanisms of phenolic building blocks is required. Interactions between various intermediates involved in the self-assembly process should be interpreted computationally. If a specific self-assembly mechanism is fully elucidated, it will greatly contribute to the commercialization of polyphenol nanoparticles for biomedical applications in the future.

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