Heliyon 8 (2022) e12497

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Supermolecules as a quality markers of herbal medicinal products

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ARTICLE INFO

Keywords:
Herbal medicinal products
Quality marker
Quality control
Small molecule
Macromolecule
Supermolecule
Self-assembly

ABSTRACT

Herbal medicines have greatly contributed to human health worldwide for thousands of years. In particular, traditional Chinese medicine plays an essential role in the prevention and treatment of COVID-19. With the exponentially increasing use and global attention to herbal medicinal products (HMPs), efficacy and safety have become major public concerns in many countries. In general, the quantification and qualification of quality markers (Q-markers) is the most common way to solve this issue. In the last few decades, small molecules, including flavonoids, terpenes, phenylpropanoids, alkaloids, phenols, and glycosides have been extensively investigated as Q-markers for HMP quality control. With the development of biotechnology in the last decade, scientists have begun to explore HMPs macromolecules, including polysaccharides and DNA, for their establishment as Q-markers. In recent years, supermolecules with stronger biological activities have been found in HMPs. In this review, we summarize and discuss the current Q-markers for HMP quality control; in particular, the possibility of using supermolecules as Q-markers based on structure and activity was discussed.

1. Introduction

Herbal medicinal products (HMPs) include herbs, herbal materials, herbal preparations, and finished herbal medicines (HMs). The term "herbal medicine" (HM) is named differently in different regions, including "Traditional Chinese medicine" (TCM) in China, "Hanfang medicine" in Japan, "Korean medicine" in Korea, "herbal medicine" in Southeast Asia, Europe, Africa, and the Arabic region, and "botanical medicine" or "natural medicine" in North America. TCM refers to drugs used under the guidance of traditional Chinese medical theory, mainly consisting of plant, animal, and mineral medicines [1]. There are more than 5000 types of TCMs used in various places, and countless prescriptions are formed by compatibility. Because plant medicines account for the majority of TCMs, they are also considered HMs [2, 3, 4]. China holds some of the largest HMPs resources and the largest trade share in the world. HMPs have been cultivated and applied in China for thousands of years, and their use in disease prevention and treatment has played an irreplaceable role in the long history of China. Because of their naturalness and fewer toxic side effects, HMPs have shown significant advantages in the treatment of many diseases and have gradually become global in recent years [5]. According to the World Health Organization statistics, approximately four billion people worldwide use HMPs to cure diseases, and the current annual sales on the international HMPs market are approximately $16 billion. Among them, Japan accounts for 80%, South Korea accounts for 10%, India, Singapore, and other countries account for 7%, and China only accounts for approximately 5% ($580 million) [6, 7, 8].

In recent years, with the gradual expansion of the scale and application of HMPs, problems, such as confusion of varieties, adulteration and counterfeiting, excessive heavy metals, and reduced efficacy, continue to occur [9]. There are many factors affecting the quality of HMPs, such as raw materials, harvesting and processing, preparation process, packaging, storage, and transportation. Meanwhile, the imperfect and unsound HMPs quality standards also lead to a lack of effective quality control [10]. The complexity of the multiple HMPs sources and origins greatly affects its quality, especially the content of active ingredients [11,

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https://doi.org/10.1016/j.heliyon.2022.e12497
Received 24 August 2022; Received in revised form 28 November 2022; Accepted 13 December 2022

12]. In 2019, the National Adverse Drug Reaction Monitoring Network in China received 89,000 reports of adverse drug reactions and events to national essential medicines of proprietary HMPs, of which 6692 cases (7.6%) were serious reports [13, 14].

Currently, quality control focuses on three aspects: determination of index ingredients, evaluation of biological activity, and evaluation of the clinical efficacy of the drug. Bioactivity determination involves evaluating and controlling the quality and activity of HMPs by comparing the specific bioeffects and biomarkers of control and test groups in organisms or isolated organs and tissues, using biostatistics as a tool, and combining the main functions or adverse effects of HMPs [15, 16]. Clinical evaluation is a factual assessment of the clinical therapeutic efficacy, adverse effects, dosing regimen, storage stability, and pharmacoeconomics of HMPs. The determination of HMPs index ingredients is an important index of quality control, which is used to study whether the active or index ingredient contents meet the medical standards [17].

Due to the complex chemical composition and unclear mechanism of HMPs, there are still some difficulties in organic integration with modern drug quality control systems. Furthermore, existing quality control models still suffer from many problems that complicate the objective evaluation and effective control of HMPs quality. To strengthen HMPs quality evaluation and establish stable and controllable quality standards, the concept of "quality marker (Q-marker) for TCMs" was perceived [18, 19, 20]. Currently, Q-markers used for the quality control of HMs mainly include small molecules (e.g., flavonoids, alkaloids, saponins, steroids, and terpenoids) and a small number of macromolecules (e.g., polysaccharides, DNA, and proteins).

In this study, the Q-markers for HMP quality control were classified and discussed according to their molecular sizes. Guided by the theory of TCM Q-markers, the feasibility of using supermolecules as Q-markers was discussed considering their chemical structure composition, pharmacological activity, and toxicity.

2. Q-marker principles

Q-markers are chemical substances inherent in HMs or formed during processing and preparation, which are closely related to functional properties. These substances reflect HMPs safety and effectiveness [21, 22, 23]. Q-markers are needed to characterize herb quality and relevance, as well as to characterize biological effects accurately and quantitatively. Herbs must also be qualitatively identified and determined via pharmacodynamic, pharmacophore, and pharmacogenetic analyses, and their safety must be tested [24, 25, 26, 27]. Q-markers based on TCMs must follow five principles: a) dissemination and traceability; b) ingredient effectiveness; c) ingredient specificity; d) ingredient testability; and e) TCM theory [28, 29]. Therefore, active, unique, toxic, and unstable ingredients are usually selected from HMPs as Q-markers. Active ingredients are used as Q-markers to study the effects of the ecological environment, construction method, and harvesting method of TCMs; toxic ingredients are used as Q-markers to study TCM contraindications; unstable ingredients are used as Q-markers to study the main biosynthetic pathways of TCM components [30, 31, 32].

2.1. Active ingredients

Active ingredients in HMPs are monomeric compounds with medical utility or physiological activity, which are important sources for the development and preparation of new drugs and play an important role in the development of innovative drugs [33, 34]. In HMP quality control, Q-markers based on active ingredients have unique characteristics and are closely related to drug efficacy. Liquid Chromatography-Mass Spectrometry, rapid chromatography, quantitative Nuclear Magnetic Resonance, and other techniques are used to quantify the active ingredients and fingerprints of HMPs to control most Q-markers [35, 36, 37].

2.2. Unique ingredients

The HMPs composition is complex, and different HMs often contain the same ingredients. For example, acteoside is found in *Callicarpa macrophylla*, *Siphonostegiae herba*, *Cistanches herba*, and *Callicarpa nudiflora*, and berberine is one of the main medicinal components of *Coptis chinensis*. Other plants also contain berberine, such as *Phellodendri chinensis*, and *Suberect spatholobus* stem [38, 39]. Specificity is an important condition for HM identification, quality evaluation, and quality control, and it provides an intrinsic basis for determining the differences in herb quality and efficacy. Scientific quality standards should be targeted and exclusive to specific HMPs. If ubiquitous ingredients are used as content determination indicators, the unique qualities of different medicinal materials cannot be evaluated accurately.

2.3. Toxic ingredients

As the use of HMPs is rapidly increasing globally, the potential toxicity of herbal drugs, in particular drug-induced liver and kidney injury, has become a serious medical issue. Toxic ingredients can be divided into exogenous (e.g., pesticide residues and heavy metals) and endogenous toxic components. Endogenous toxic components can be strictly toxic (e.g., aristolochic acid) or toxic but also effective (e.g., aconitine) [40, 41, 42].

2.4. Unstable ingredients

Drug stability and degradation studies are integral to drug quality control. Pharmaceutical preparations containing unstable ingredients are susceptible to degradation or transformation under various environmental conditions, such as temperature, light, and storage environment, resulting in changes in their quality and reduced drug potency over time [43, 44]. Harish et al. [45] showed that deterioration of unstable components during storage of HMs posed a threat to the production and safety of HMs. Thus, the analysis and study of unstable ingredients are of great importance for HMPs quality assurance and evaluation. Therefore, in addition to demonstrating the properties of unknown ingredients as much as possible, the properties, action laws, efficacy, and toxic side effects of degradation products must be studied in HMs containing ingredients with poor stability [46].

3. Small molecules as Q-markers

Small molecules are organic compounds with small molecular weights, usually biofunctional molecules of $<$1000 Da (especially $<$400 Da) [47]. Small molecule Q-markers currently used for quality control include flavonoids, terpenes, phenylpropanoids, alkaloids, phenols, glycosides, and quinones. Detailed information on Q-markers in pharmacopoeias of different countries and regions is summarized in Table 1 and Supplementary Tables S1-7 [48, 49, 50, 51, 52, 53, 54]. As shown in Figure 1(A, B), we deduced that flavonoids, terpenes, and phenylpropanoids were the top three Q-markers used for quality control.

3.1. Flavonoids

Flavonoids are an important class of components that are diverse, widely present in nature, and have a wide range of biological activities [55]. In the Chinese Pharmacopoeia (CP, 2020 edition), there are 89 and 88 HMs with flavonoids as quantitative and qualitative Q-markers, respectively. These quantitative and qualitative Q-markers, respectively, represent 13 and 8 entries in the Korean Pharmacopoeia (KP, 10th version), 16 and 36 in the Japanese Pharmacopoeia (JP, 17th version), 34 and 50 in the European Pharmacopoeia (EP, version 10.0), 38 and 29 in the United States Pharmacopoeia (USP, 2021 edition), 44 and 66 in the British Pharmacopoeia (BP, 2020 edition), and 47 and 49 in the Hong Kong Chinese Materia Medica Standards (HKCMMS, version 10.0).

Table 1. Q-marker for quantification and qualification in pharmacopoeias of different countries and regions.

	Pharmacopoeia of the People's Republic of China (2020)		The Korean Pharmacopoeia (Tenth edition)		The Japanese Pharmacopoeia (Seventeenth edition)		European Pharmacopoeia (Tenth edition)		The United States Pharmacopoeia (2021)		British Pharmacopoeia (2020)		Hong Kong Chinese Medicinal Materials Standards (Volume X)	
	quantitative indicators	qualitative indicators	quantitative indicators	qualitative indicators	quantitative indicators	qualitative indicators	quantitative indicators	qualitative indicators	quantitative indicators	qualitative indicators	quantitative indicators	qualitative indicators	quantitative indicators	qualitative indicators
Flavonoids	89	88	13	8	16	36	34	50	38	29	44	66	47	49
Terpenoids	83	89	20	13	46	36	20	36	71	40	39	64	51	56
Phenyl-propanoids	68	71	17	4	22	27	30	51	35	46	33	54	66	44
Alkaloids	55	54	17	5	29	20	25	23	37	23	50	39	36	35
Phenols	38	40	9	2	13	31	23	19	20	22	33	29	23	22
Glycosides	25	26	7	5	16	21	16	20	34	22	11	15	14	15
Volatile Oils	22	22	4	1	10	14	7	3	4		2	2	12	
Quinones	9	8	5	3	8	10	6	5	6	2	11	6	6	6
Organic acids	6	1	4		3		2	2	9	3	2			
Poly-saccharides	12	12	1		1		2	2	2				6	5
DNA	1												1	
Amino Acids		4		4				2		3				1

3.2. Terpenes

Terpenoids are a class of natural products comprising numerous species, large quantities, complex structures, abundant resources, and significant biological activities in nature. They are also a class of active ingredients in TCMs. To date, nearly 30,000 terpenoids have been discovered [56]. In CP, HMs with terpenes as quantitative and qualitative Q-markers include 83 and 89 entries, respectively, followed by 20 and 13 in KP, 46 and 36 in JP, 20 and 36 in EP, 71 and 40 in USP, 39 and 64 in BP, and 51 and 56 in HKCMMS.

3.3. Phenylpropanoids

Phenylpropanoids are a class of natural compounds containing one or several C_6–C_3 units in their structure. These components are widely found in TCMs, and they exhibit various physiological activities [57]. In CP, HMs with phenylpropanoids as quantitative and qualitative Q-markers include 68 and 71 members, respectively, followed by 17 and 4 in KP, 22 and 27 in JP, 30 and 51 in EP, 35 and 46 in USP, 33 and 54 in BP, and 66 and 44 in HKCMMS.

3.4. Alkaloids

Alkaloids are a class of natural nitrogen-containing alkaline organic compounds, which are also referred to as pseudo-alkaloids. Most have a complex ring structure, mostly containing nitrogen, which has remarkable biological activity and is an important active ingredient in TCMs [58]. In CP, HMs with alkaloid quantitative and qualitative Q-markers include 55 and 54 members, respectively, followed by 17 and 5 in KP, 29 and 20 in JP, 25 and 23 in EP, 37 and 23 in USP, 50 and 39 in BP, and 36 and 35 in HKCMMS.

3.5. Phenols

Phenols are hydroxyl-containing derivatives of aromatic hydrocarbons. Most phenolic compounds present in nature are a result of plant activities. Phenols contained in plants are named endogenous phenols, whereas the rest are named exogenous phenols. Phenolic compounds have a particular aromatic odor, are weakly acidic, and are easily oxidized in the environment [59]. In CP, HMs with phenols as quantitative and qualitative Q-markers include 38 and 40 entries, respectively, followed by 9 and 2 in KP, 13 and 31 in JP, 23 and 19 in EP, 20 and 22 in USP, 33 and 29 in BP, and 20 and 22 in HKCMMS.

3.6. Glycosides

Glycosides are compounds that contain links between sugars or derivatives of sugars, such as amino sugars and uronic acids, and another type of non-sugar substance through the terminal carbon atom of the sugar [60]. In CP, HMs with glycosides as quantitative and qualitative Q-markers include 25 and 26 entries, respectively, followed by 7 and 5 in KP, 16 and 21 in JP, 16 and 20 in EP, 34 and 22 in USP, 11 and 15 in BP, and 14 and 15 in HKCMMS.

3.7. Quinones

Quinones are a class of chemical constituents with quinoid structures present in TCMs, which are mainly divided into four types: benzoquinone, naphthoquinone, phenanthrenequinone, and anthraquinone. Anthraquinone and its derivatives are important in TCMs [61]. In CP, HMs with quinones as quantitative and qualitative Q-markers of 9 and 8, respectively; 5 and 3 in KP; 8 and 10 in JP; 6 and 5 in EP; 6 and 2 in USP; 11 and 6 in BP; and 6 and 6 in HKCMMS.

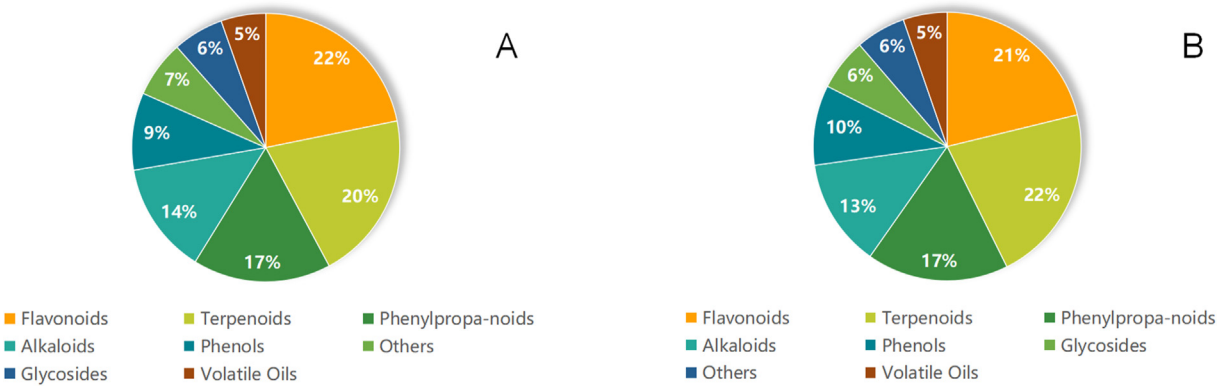

Figure 1. Proportion of Q-markers in Pharmacopoeias of the People's Republic of China (2020) A: quantitative indicators, B: qualitative indicators.

3.8. Others

Other small molecules, such as organic acids and amino acids, have also been documented in national pharmacopoeias as qualitative and quantitative Q-markers. In CP, HMs with organic acids as quantitative and qualitative Q-markers include 6 and 1 entries, respectively; in KP, there are 4 quantitative Q-markers; in JP, there are 3 quantitative Q-markers; in EP, the quantitative and qualitative Q-markers are 2 each; in USP, the quantitative and qualitative Q-markers are 9 and 3, respectively; and in JP, there are 2 quantitative Q-markers. The number of amino acids in the HMs recorded as qualitative Q-markers in CP, KP, EP, USP, and HKCMMS is 4, 4, 2, 3, and 1, respectively.

4. Macromolecules as Q-markers

Macromolecules refer to a variety of organic molecules with a molecular weight of tens of thousands or more that are the main active ingredients in living organisms [62]. In recent years, macromolecules have gradually become quality control, mainly including polysaccharides, DNA, and proteins (Table 1 and Supplementary Tables S1-7).

4.1. Polysaccharides

Polysaccharides are formed through condensation and dehydration of multiple monosaccharide molecules. All carbohydrates and their derivatives that conform to the concept of polymer compounds are referred to as polysaccharides [63]. HMs with polysaccharide components as quantitative Q-markers were recorded in the CP including 12 species, as well as 1 in KP, 1 in JP, 2 in EP, 2 in USP, and 6 in HKCMMS. The number of qualitative Q-markers in CP, EP, and HKCMMS is 12, 2, and 5, respectively.

4.2. DNA

DNA is a nucleic acid, one of the four biological macromolecules contained in biological cells. DNA carries the genetic information necessary for RNA and protein synthesis and is an essential biological macromolecule for the development and normal functioning of organisms [64]. CP recorded only one TCM, *Dendrobium nobile Lindl*, which uses DNA as a quantitative Q-marker.

4.3. Proteins

Proteins are biomolecules with a certain spatial structure formed by the coiled folding of a polypeptide chain composed of amino acids, and they are an important component of all cells and tissues in the human body. In general, proteins account for approximately 18% of the total mass of the human body, and most importantly, hold great relevance to the phenomenon of life [65]. CP has recorded only one TCM, *Omphalia Polyporus mylittae Cood. Et Mass.*, which uses a protease as a quantitative Q-marker.

5. Advantages of supermolecules

Supermolecules consist of two or more molecules bound together through intermolecular interactions to form complex and organized aggregates that maintain a certain integrity to develop a well-defined microstructure and macroscopic properties [66, 67]. The term supermolecule was introduced in the mid-1930s, and the concept of supramolecular chemistry was first proposed in 1987 by the French scientist J. M. Lehn, a Nobel laureate in chemistry. Supramolecular chemistry is the chemistry of molecular aggregates based on non-covalent interactions between molecules; in other words, intermolecular interactions form the core of supramolecular chemistry [68, 69]. At present, these aggregates can be divided into two categories: supermolecules formed by the self-assembly of two small molecules and supermolecules composed of small molecules and inorganic complexes [70].

5.1. Small molecule self-assembly

Self-assembly is the formation of a stable, structured, and self-assembled system through the weak interactions of non-covalent bonds, such as hydrogen bonds, van der Waals forces, π-π stacking, electrostatic interactions, and ligand bonds [71, 72]. Especially for intermolecular hydrogen bonds, self-assembly forces mainly involve synergistic interactions between hydrogen bonds or between hydrogen bonds and other non-covalent bonds [73, 74, 75]. At present, several supermolecules formed by the self-assembly of small molecules have been discovered in TCMs, and their preparation includes berberine and rhein, berberine and baicalin, and berberine and cinnamic acid, which possesses stronger activities and lesser toxicities.

5.2. Enhanced antibacterial activity

Berberine, a quaternary amine isoquinoline alkaloid, mainly exists in the Berberidaceae, Papaveraceae, Rutaceae, and Menispermaceae families and the *Ranunculus* genus, which has antibacterial, antiviral, antidiabetic, anti-inflammatory, and antitumor activities. However, berberine is poorly water soluble and has a bitter taste [76, 77]. To improve the solubility and bioavailability of berberine, it is often self-assembled with the active molecules of other TCMs to form nanoparticles for the treatment of various diseases. Based on the idea of supramolecular chemistry in TCMs, researchers have prepared self-assembled nanoparticles by combining berberine with rhein [78], baicalin [79], cinnamic acid [80], 3,4,5-trimethoxycinnamic acid [81], glycyrrhiza protein [82], and glycyrrhizic acid [83] through intermolecular hydrogen bonding. Compared with berberine alone, the antibacterial activity of nanoparticles was enhanced [84, 85], berberine half-life was prolonged, adverse reactions were

reduced, and the bitter taste was weakened [86]. Similarly, self-assembled supermolecules of berberine and baicalin also showed good neuroprotective activity, which was protective against nerve growth factor-induced PC12 cell injury [87].

5.3. Improved anticancer efficiency

Paclitaxel, a complex secondary metabolite isolated from *Taxus chinensis (Pilger) Rehd.*, has become a broad-spectrum anticancer drug with strong activity widely used in the treatment of breast cancer, ovarian cancer, and lung cancer [88]. However, due to its poor water solubility and low oral bioavailability, it requires assistance from drug delivery systems. Some researchers have also prepared highly drug-loaded self--assembled nanoparticles from paclitaxel-berberine [89] and paclitaxel-ursolic acid [90] via hydrogen bonding and hydrophobic interactions. The nanoparticles not only demonstrated the excellent anticancer activity of paclitaxel, but also exerted the antibacterial effect of berberine or the hepatoprotective effect of ursolic acid. Similarly, self-assembled nanoparticles of ursolic acid molecules [91] and self-assembled nanoparticles of poricoic acid A also showed strong anticancer activities, which were significantly enhanced compared with those of free drugs [71]. It has been found that dehydrotrametenolic acid can form nanoparticles through intermolecular hydrogen bonding. It can be administered orally to effectively deliver hydrophilic or hydrophobic drugs, enhance gastrointestinal permeability, and significantly improve oral drug bioavailability in cancer therapy [92]. Dai et al. [93] prepared novel nanoparticles with uniform particle size distribution, high efficiency, anticancer efficiency, and biocompatibility based on the self-assembly of ginsenoside Rb1 and protopanaxadiol, which prolonged *in vivo* circulation time and enhanced bioavailability.

5.4. Toxicity reduction

Some natural HMs that self-assemble to form nanoparticles can also reduce toxicity. Studies have reported that berberine and rhein interact with each other to form supermolecules during the co-decoction of rhubarb and *Coptis chinensis*, and combined decoction showed less bitterness, no obvious diarrhea symptoms, and less pathological damage to the colon [86]. The gel formed by the self-assembly of rhubarb acid could achieve the same toxicity reduction effect [94]. Epigallocatechin gallate (EGCG) is an antioxidant polyphenolic flavonoid compound that exerts antitumor effects by inhibiting telomerase and DNA methyltransferase activity. Zhang et al. [95] demonstrated that carrier-free self-assembled nanoparticles composed of ursolic acid and EGCG could reduce side effects, such as low drug load and potential toxicity. Wang et al. [96] demonstrated that nanoparticles of oleanolic acid and glycyrrhetinic acid self-assembled through non-covalent interactions could reduce the liver damage caused by chemotherapeutic drugs by upregulating key antioxidant pathways, compared with free drugs.

5.5. Self-assembly of small molecules and inorganic substances

In addition to the self-assembly of small molecules, some natural products can form supermolecules through coordination with inorganic complexes. Luteolin and quercetin are flavonoids present in a variety of herbs, including honeysuckles and Herba Ajugae, with various pharmacological properties, including anti-inflammatory, anti-allergic, antitumor, antibacterial, and antiviral effects [97, 98]. They are readily available with good biocompatibility and low toxicity; however, poor solubility and biostability hinder their application in biomedicine. Liu et al. [99] used luteolin and Fe^{3+} as building blocks to prepare stable nanoparticles. Compared with luteolin alone, the obtained nanoparticles showed higher solubility and greatly enhanced antioxidative stability. Importantly, Fe^{3+}-coordinated nanoparticles exhibited supramolecular photothermal effects, enabling them to function as photothermal agents. Han et al. [100, 101] prepared self-assembled supermolecules of quercetin with six metal ions, which exhibited enhanced DPPH scavenging activity, DNA cracking activity, and antitumor activity.

Catechins are a class of phenolic active substances extracted from plants, which have various pharmacological properties, such as antitumor, antioxidative, and antibacterial effects and protection of the heart and brain organs. Fei et al. [102] prepared catechin-Ag nanoparticles containing core-shell nuclei using a molecular self-assembly strategy under microwave radiation, where the catechins were oxidatively cross-linked using $AgNO_3$ and self-assembled into shells around the Ag nanocore. The study found that these nanoparticles could strongly inhibit *Escherichia coli* growth, with no obvious toxicity to normal cells, indicating their great potential as selective antibacterial nanomaterials for biomedical applications.

6. Discussion

In the beginning of HMPs investigation, small molecules, including flavonoids [55], terpenes [56], phenylpropanoids [57], alkaloids [58], phenols [59], and glycosides [60]. was widely attracted scientist's attention, and they were subsequently was been used as Q-markers for HMP quality control due to the effective. Macromolecules, particularly polysaccharides, were considered as useless components of HMPs. With the development of biotechnology in the recent decade, the interests in macromolecules, particularly polysaccharides [63], are increasing rapidly. Polysaccharides display various activities including antitumor, immunoregulatory, anti-diabetes, and anticoagulant activities; therefore, they have been gradually adapted as Q-markers for HMP quality control. Recently, some scientists found the present of supermolecules in HMPs with stronger activities, such as antibacterial [76, 77, 78, 79, 80, 81, 82, 83, 84, 86, 87], anticancer [71, 88, 89, 90, 91, 92, 93], and toxicity reduction [86, 94, 95, 96], which is the promising Q-markers for HMP quality control.

7. Conclusions and prospects

Supermolecules show better bioactivity and higher toxicity reduction and potentiation effects, and they can achieve highly stable drug delivery. Currently, self-assembly forces between supermolecules are mainly based on non-covalent forces and thus have poor stability, which is consistent with the characteristics of activity, toxicity, and instability of the index components; therefore, they can be used as Q-markers to control HMPs safety and efficacy. However, some issues remain unresolved. First, the composition of TCMs compounds is complex, and the technology for separation of their active ingredients is still immature, making it difficult to identify and separate various active supermolecules. Second, supermolecules show good activity *in vitro* and *in vivo*; however, it is uncertain whether they still exist in the form of supermolecules *in vivo*. Third, the detection of supermolecules is problematic, because chromatographic separation can destroy their structures. Mass spectrometry imaging as a technical tool to detect and achieve precise localization of supermolecules *in vivo* remains to be studied. In conclusion, we summarize and discuss the principle of Q-marker and the current Q-markers for HMP quality control; Based on the pharmacological activity of supermolecules, we strongly believe that supermolecules will attract more attention in research with a focus on their use as Q-markers for HMP quality control in the future. In a word, small molecules were the hot spots in the past; macromolecules are the hot spots in the present, and supermolecules will be the hot spots in the future, which means that all of those molecules, including small molecules, macromolecules, and supermolecules will be used as Q-markers for HMP quality control in the future.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

Wei Cai was supported by the Science and Technology Innovation Program of Hunan Province (no. 2022RC1228), Hunan University of Medicine high-level talent introduction startup funds (15001) and Hunan Province Social Science Innovation Research Base (Ethnic medicine and ethnic culture research base).

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e12497.

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