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Encapsulation of polyphenolic compounds for health promotion and disease prevention: Challenges and opportunities

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ABSTRACT

Polyphenolic compounds are present in different parts of plants, including the root, stem, bark, leaves, seeds and fruits. They have been reported for their various biological functions including antimicrobial, antioxidant, anti-inflammatory, anticancer, antidiabetic, cardioprotective, and neuroprotective effects to mention a few, based on their interesting structures. The structure-function relationship of these polyphenolic compounds confers nutraceutical potentials on them, thus making them suitable for novel drug design and formulation of pharmaceutics. However, to preserve the structural properties of these polyphenolic compounds in biological systems, they have to be encapsulated in matrix of biopolymers. Hence, the need for the technology of nanoencapsulation that will enable the preservation and protection of the polyphenolic compounds from degradation and loss of potency. This review captures nanoencapsulation technology of polyphenolic compounds, their application in food and pharmaceutical industries, safety and biocompatibility. This also describes the health promotion and disease prevention of encapsulated polyphenolic compounds in animals and humans.

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1. Introduction

Polyphenols can be found in a wide range of medicinal plant species in their natural state. Polyphenol concentration in some plant-based foods can be as high as 500 mg per 100 g of food [1]. Colored fruits (particularly small berries), whole-grain cereals, cocoa, coffee, and red wine, as well as apples, oranges, and green beans, are the best sources of dietary polyphenols [2]. Polyphenolic compounds are naturally-occurring bioactive compounds with widely studied health-promoting properties. Polyphenols are partially responsible for the color, taste, and organoleptic qualities of foods, in addition to their protective functions [3]. They are a collection of chemically different plant-derived compounds that are identified by the presence of hydroxylated phenyl moieties. The majority of polyphenols in plants are glycosylated [4].

Several studies have found a link between polyphenol consumption and the risk of major diseases such cancer, cardiovascular disease, type 2 diabetes, neurological diseases, and osteoporosis [5]. The action of polyphenols as strong effectors of biologic processes linked to the etiology of human diseases explains this association. Polyphenolic compounds have anti-allergenic, anti-atherogenic, anti-inflammatory, antibacterial, antioxidant, cardioprotective, and vasodilatory activities, among others [6, 7]. The high free radical scavenging effect of polyphenols, owing to their capacity to donate

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hydrogen atoms or electrons, is arguably the best studied aspect of their properties and functions [8].

It is worth remembering that the efficacy of nutraceutical products in preventing disease is contingent on the active compound's bioavailability being preserved. As a result, oral administration of polyphenols requires additional protection in order to maintain structural integrity and maximize bioavailability, making encapsulation, particularly nanoencapsulation, the solution of choice [9].

Generally speaking, encapsulation and nanoencapsulation processes are used to stabilize and control the release of core material and to separate reactive or incompatible components of formulation [10]. Nanomaterials and nanocarrier systems provide many advantages by means of protecting sensitive food or drug components, ensuring against nutritional loss, incorporate pulsative or time-release mechanisms into the formulation, mask or preserve flavors and transform liquids into easily handled solid ingredients. Towards this end, liposomes, nanoliposomes, niosomes and tocosomes are among the most applied encapsulation / nanoencapsulation systems [11-14].

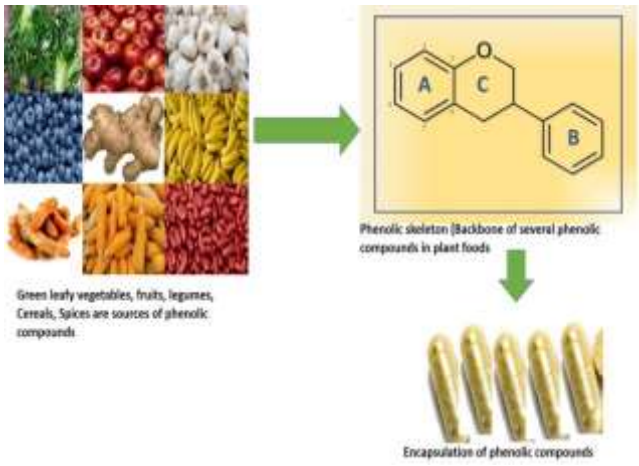

Fig. 1. General chemical structure of typical polyphenols, their sources and a potential application [15].

Thousands of polyphenolic compounds have been classified into several classes based on differences in their chemical skeletons, such as degrees of oxidation, hydroxylation, methylation, glycosylation, and probable linkages to other molecules (Figure 1). Polyphenols are classified in different groups as depicted in Figure 2. Flavonoids (including the subclasses anthocyanidins, catechins, flavones, flavanols, flavanones, and isoflavones), coumarins, stilbenes, and tannins are the four classes of polyphenols, however other elements such as chalcones and lignans have polyphenolic structures [16].

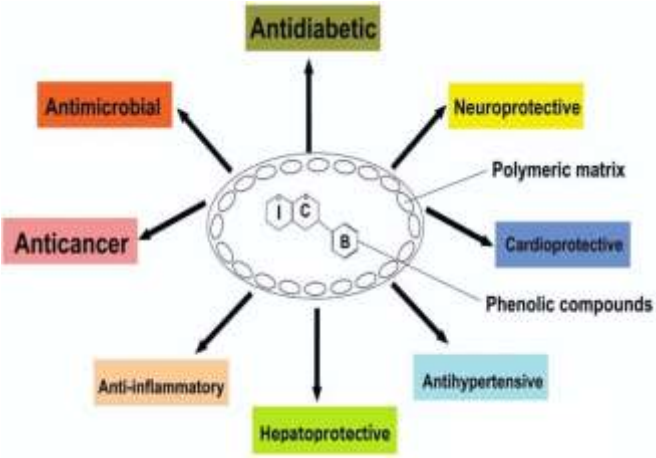

Fig. 2. The main therapeutic applications of polyphenols [15].

2. Encapsulation of polyphenolic compounds

The entrapment of a core material (bioactive molecule, inner phase, or payload phase) within another immiscible substance (carrier or wall), which might be solid or liquid, is known as encapsulation. The encapsulation method selected is determined by the core material and the desired qualities of the final product. It is important to know that the carrier composition influences the final properties of the product, effectiveness of the encapsulation method and release of the compounds from its entrapment. Among all the properties of the final product affected, the most important are water solubility, shelf life and bioavailability [17].

There are two types of encapsulation strategies in term of the size of the produced carrier, namely micro and nanoencapsulation. Notwithstanding the benefits of nanoencapsulation, microencapsulation methods remain the most widely used methods. This includes physical methods like spray drying, fluid bed coating, extrusion, co-extrusion, molecular encapsulation, and emulsions [18]. In terms of size, nanoparticles (NPs) range from 1 nm up to <1 μm, whereas microparticles range from 1–800 μm. Considerable increase in surface to volume ratio is

the reason for the many advantages of nanoencapsulation [19].

3. Materials for encapsulation

Polysaccharides, proteins and lipids are the matrices available as options to protect and deliver bioactives. Choosing the adequate protective matrix is based on desired properties and the use of the product. Polysaccharides are the main polymeric matrix used; they are obtained from various sources, and are biodegradable, biocompatible, and nontoxic [20]. Some of the most applied polysaccharides are maltodextrin, starch, pectin, chitosan, alginate, and gums. Maltodextrin are more effective than inulin to carry and deliver anthocyanins, polyphenols, and protect antioxidant activity of blackcurrant extracts [21]. Sometimes when two or more carrier materials are combined it can improve physicochemical characteristics of the carrier system, for example maltodextrin/pectin particles of herbal extracts maintains the antioxidant activity during 6 months of storage of various sample [22].

The proteins that are widely used as carrier materials are maize zein, gelatin, and whey protein. On the other hand, the most commonly employed phospholipid for the manufacture of lipidic carrier systems is lecithin (phosphatidylcholine), that is immiscible with water and is inexpensively isolated from soya beans or egg yolk [23]. As earlier discussed, different materials can be used to encapsulate bioactive compounds and rationale selection of ingredients and excipients is important to obtain product of interest.

4. Methodologies for encapsulation

Different encapsulation strategies can protect specific natural compounds, such as carotenoids, phenolic compounds (polyphenols), phytosterols, and probiotics. An adequate selection depends on the active compound to protect, as formation and rheological properties of most encapsulation systems strongly depend on interactions between carrier and core materials [24]. The most used encapsulation techniques are spray drying, freeze-drying, emulsions, nanoprecipitation, liposomes, and niosomes, while the main polymeric matrices are polysaccharides and polypeptides [14].

Encapsulation is essential for preventing the degradation of bioactive substances. Microencapsulation and nanoencapsulation are the main two types of encapsulation currently available. Nanoencapsulation is chosen over microencapsulation because of its nano-scale size, as the smaller the capsules are, the higher their bioavailability and the more easily their release may be adjusted and controlled. The encapsulation method is chosen based on two key factors: (a) the nature of the core material; and (b) the nature of the wall material, which includes its size, thickness, solubility, permeability, and delivery rate [23]. The three primary classifications are chemical (emulsion and interfacial polymerization), physical–chemical (emulsification and coacervation), and physical–mechanical methods (spray drying / spray-cooling / spray-congealing / prilling, freeze-drying, electrodynamic processes, and extrusion) [13].

5. Microencapsulation of phenolic compounds

Microencapsulation is a new technology that allows food components or functional constituents to be protected from various processing conditions by entrapping them in a polymeric or nonpolymeric substance and allowing for controlled release under specific conditions. Coating materials are chosen based on their rheological qualities, ability to distribute and stabilize the active molecule, inertness to the active compound, and ability to correctly store the active compounds. Some of the carrier materials include lipids such as wax, paraffin, beeswax, diacylglycerols; proteins such as glutein, casein, gelatin; carbohydrates such as starch, maltodextrin, modified starch, cyclodextrin, cellulose and gums such as gum acacia, agar and carrageenan. Spray chilling, spray cooling, fluidized bed coating, liposome entrapment, extrusion, freeze drying, and coacervation are just a few of the microencapsulation techniques available [25].

6. Nanoencapsulation of phenolic compounds

Nanoencapsulation is recommended over microencapsulation because of its nano-scale size, as the smaller the capsules are, the higher their bioavailability and the more easily their release may be adjusted and controlled [26]. NPs are colloidal-sized particles with diameters ranging from 10 to

999 nm and are expressed both as nanocapsules and nanospheres [27-29]. It is a technique in which bioactive substances are encapsulated using an appropriate nano-carrier that is resistant to enzymatic degradation, particularly in the gastrointestinal tract, such as zein, chitosan, or alginate polymers. Furthermore, these wall materials assist in sustaining the compound's nutritional function as well as concealing the unpleasant taste of some compounds. The technique employs several delivery methods such as NPs, nanolaminates, nanofibers, nanotubes, self-assembled nanostructures, nanoemulsions, association colloids [26, 30].

7. Encapsulation of phenolic compounds for therapeutic aspects

Encapsulation is a technique that protects the compound, so using it on compounds whose chemical structure and/or biological activities are easily lost is the most appropriate application of this methodology. Polyphenols are known for their health-promoting effects but have very low shelf life because of their sensitivity to light, oxygen, pH, and temperature changes [31]. The subsequent paragraphs highlight medicinal / therapeutic applications of encapsulation of phenolic compounds as functional food and nutraceuticals.

7.1. Diabetes

Phenolic compounds have been linked to a variety of biological features, including antioxidant, antibacterial, anti-cancer, anti-inflammatory, and anti-diabetic activities [32]. Diabetes chronic disease is a health condition that affects a growing number of people globally [33]. With increasing annual statistics of affected population worldwide, it is projected that at least 400 million people will be diagnosed with diabetes by 2030. Oxidative stress has been identified as an important precursor in the pathogenesis of diabetes whereby reactive oxygen species that are not neutralized result in the formation of immune complexes and inflammatory reactions. The antioxidant activity of phenolic materials against oxidative stress has therefore been investigated in the treatment/management of diabetes. These compounds are also thought to possess anti-diabetic properties by increasing insulin secretion, insulin sensitivity, and insulin-dependent glucose uptake, inhibiting glucose absorption in the intestine by sodium-dependent glucose transporter 1 (SGLT1), lowering hepatic glucose output, and influencing the gut microbiome [34].

Anthocyanins, a polyphenol have been shown to block the enzymes -amylase and -glucosidase, resulting in the reduced metabolism of carbohydrate in monosaccharides, thus, preventing their absorption [35]. The ability of dietary polyphenols to maintain glucose homeostasis suggests that they may be useful in the prevention and management of diabetes. However, there are various obstacles in the way of reaching this goal. While several fundamental research and clinical trials have revealed the health benefits of polyphenols relative to their anti-diabetic effect in both healthy and diseased population, the results are conflicting due to different reasons. For instance, the concentration of polyphenols used in in-vivo and in-vitro studies to demonstrate anti-oxidant activities is typically higher than the average concentration found in human diet; most importantly, the compounds' ability to exert effect in target tissues is significantly reduced due to their low bioavailability in humans [5]. While there are various extrinsic factors that might affect polyphenol bioavailability, such as dietary matrix, gut bacteria, and quick elimination, intrinsic limitations such as decreased water solubility, instability at low pH, and particle size are some of the most significant obstacles [36]. As a result, the use of nanomaterials to boost polyphenol bioavailability is becoming increasingly popular because methods employed in the synthesis of nanosystems have the potential to change the physical and chemical properties of polyphenols, thus, increasing their bioavailability.

In order to evaluate the effects of nanopolyphenols in diabetic animals, researchers used a variety of polyphenols and nanocarriers. Nanotechnology has proven to be a promising field for addressing these issues by increasing bioavailability and enabling for tailored medication delivery and prolonged drug release while lowering therapeutic dose requirements [37].

Rambaran (2020), carried out extensive research on the effect of encapsulation on the treatment of diabetes using different methods. Results indicated that nanotechnology enhanced the therapeutic

potential of polyphenols in the treatment of diabetes regardless of the difference in the type of polyphenol selected for the experiment, the nanocarrier and nanoencapsulation technique employed, the size of the nanomaterials, the drug delivery system, the dose of nanopolyphenol administered, the encapsulation efficiency and loading capacity of the resulting nanomaterials, and the study duration [38]. Despite these differences, the nanopolyphenols' anti-diabetic benefits were significantly evident in all but 4 of the 33 studies evaluated. This corresponds with the findings of Medina-Pérez et al. (2020), whose experiment on the encapsulation of phenol-enriched citrus fruit revealed that in addition to its antidiabetic and antioxidant potential, microencapsulation of xoconostle extract utilizing a double emulsion technique could be an effective option for the preservation of primary and secondary metabolites of xoconostle, as it keeps 60–80 percent of the bioactive chemicals alive [39].

Lei Chen et al., (2019) also reported that instead of using free chemicals, microencapsulated polyphenols can effectively address the deficits [40]. The findings so far show that encapsulation improves the protection of active chemicals, paving the way for industrial uses of active packaging. Gallic acid, for instance, is a potent antidiabetic phenolic compound; however, the rapid breakdown of the compound throughout the absorption process has limited its efficacy, producing disappointing outcomes. To address this deficit, Purbowatiningrum and co-workers (2017) examined the encapsulated in nano-chitosan [41]. Freeze-drying method was used to encapsulate the compound into chitosan NPs, which serves to protect the bioactive compound from degradation, boost solubility, and deliver the bioactive compound to the target site. Scanning electron microscopy (SEM) analysis of chitosan NPs revealed that their size is homogeneous and smaller than that of chitosan. Gallic acid encapsulated within chitosan NPs has encapsulation efficiency (EE) of about 50.76 percent. Gallic acid-chitosan NPs at 50 ppm were shown to inhibit -glucosidase activity in 28.87 percent of cases, with an IC50 of 54.94. As a result, it can be inferred that gallic acid can be encapsulated in chitosan NPs and that it can block glucosidase, thus, presenting encapsulated gallic acid as a potential candidate in the development of antidiabetic therapy [41].

7.2. Alzheimer's disease

Alzheimer's disease (AD) is characterized by a progressive loss of cognitive abilities caused by the accumulation of large aggregates of amyloid-beta 42 (Aβ42), the formation of neurofibrillary tangles of hyper-phosphorylated forms of microtubule-associated tau protein, leading to a variety of cellular and systemic level alterations [42]. Currently, rather than delivering a possible cure, present therapy strategies generally focus on reducing disease symptoms. The ability of most drugs to pass the blood–brain barrier (BBB) is a major challenge, hence the resolve to Nanotechnology-based treatments which in turn have provided an alternative platform to address the problem of drug delivery to specific targets. Phenolic compounds due to their anti-oxidant and anti-inflammatory properties have been implicated positively in the treatment of AD and hence the reason why nutraceuticals are considered as a major combatting strategy for AD. Inclusion of epicatechin and other flavonoid inhibitors of the β-site APP cleaving enzyme 1 (BACE1) proteolysis/cleavage of certain active compounds (e.g. quercetin, myricetin, catechins, tannins, anthocyanidins, resveratrol, and ferulic acid) in diet may protect against early amyloidosis events in AD [43]. To reduce the chances for development of AD, increased consumption of flavonoid and polyphenol is a dietary preventative strategy to minimize the formation of amyloid and competitively prevent amyloid misfolding and toxicity [44]. For the effectiveness of this strategy, there is need for encapsulation of these phenolic compounds that have been reported to play crucial role in AD. Encapsulation helps preserve their biological activity and bioavailability, thus playing a key role in AD prevention and treatment. Prasanna and Upadhyay (2021) reported that combining the potential applications of flavonoids (which are phenolic compounds) with nanaomedicinal approaches might result in highly therapeutic efficacy in combating well-known neurodegenerative diseases [45].

7.3. Cancer

Phenolic compounds such as curcumin, resveratrol (3,5,4'-trihydroxystilbene), kaempferol, epigallocatechingallate (EGCG), apigenin and quercetin (3,3′,4′,5-7-pentahydroxyflavone) have been reported to play a vital role as pro-oxidants in the prevention of cancer development because of their intense reactive oxygen species (ROS) scavenging activity, hence resulting in apoptosis of cancer cells [46]. Other mechanisms of phenolic compound anti-cancer efficacy include: inhibition of insulin-like growth factor reported to be an important factor in the development of many cancers, including breast, lung, and colorectal cancer as well as modulation of some of the signal transduction pathways related to the cancer process, modulation of proinflammatory cytokines and modulation of several apoptotic proteins like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), cyclooxygenase-2, signal transducer and activator of transcription 3 (STAT3), and endothelin-1 [47]. Additionally, isoflavones have been reported to have multifunctional actions against cancer, such as inhibiting hormone-dependent malignancies and changing the expression of estrogens receptors, tumour suppressors, and transcription factors in cancer cells [48]. Although the potential effectiveness of polyphenolic compounds against diverse types of cancer have been reported by various researchers, they are limited in clinical use due to shortcomings such as poor pharmacokinetics, poor water solubility and low stability, a viable approach in this field is to utilize a variety of encapsulation approaches, particularly new nanocarrier systems [49]. Data from previous researches revealed that polyphenols' cytotoxicity against cancer cells are linked to their relatively high concentration. Because of the safety risks associated with the use of high dosages of polyphenols, tailored delivery strategies are required for effective anticancer efficacy. These nanocarriers have been reported to provide a regulated release and increased curcumin bioavailability [50]. Moreover, the study of Baek and Cho (2017) who evaluated the anticancer activity of solid lipid nanoparticles (SLN) loaded with curcumin revealed that the curcumin encapsulated in the nanocarrier significantly increased cellular absorption and cytotoxicity in MCF-7 cells, as well as lymphatic uptake and oral bioavailability [51]. Quercetin, curcumin, and EGCG encapsulated in nanostructures were also found to inhibit NF- signaling and induce apoptosis in some cancer models [52]. Furthermore, the metabolic and anticancer effects of resveratrol-loaded poly ethylene glycol-poly lactic acid (PEG-PLA) NPs were explored in CT26 colon cancer cells in mice in a study conducted by Jung and co-workers. When compared to animals treated with empty NPs, the results showed a considerable tumour growth inhibition of 67 percent [53]. Findings from available literatures therefore suggest that encapsulation of phenolic compound could represent novel approaches to cancer prevention and treatment, with potential biomedical applications.

7.4. Hypertension

Hypertension has been linked to several cardiovascular diseases, such as coronary heart disease, heart failure, myocardial infarction, stroke and end-stage renal disease, and is one of the leading causes of death worldwide. The etiology of hypertension is multi-factorial and eating habits have been recurrently noted as an important risk factor that contributes to the progression of the disease [54]. Several studies have established the use of dietary supplements and nutraceuticals in the prevention and treatment of these diseases chiefly because they confer physiological benefits and protect against a host of chronic diseases [55]. Some of these nutraceuticals are abundant in phenolic compounds which have been reported to express cardioprotective activity such as potential vasodilator, antiplatelet, and ability to lower blood pressure and LDL (low-density lipoprotein)-cholesterol, thanks to their bioactive constituents. Flavanols, flavan-3ols, flavanones, flavones, chalcones are classes of phenolic compounds that have been reported to show anti-hypertensive effect [56].

The various mechanisms by which phenolic compounds exert cardioprotective activities are; via endothelial nitric oxide synthase (eNOS) effects, gene expression, catalysis activation by phosphorylation of the eNOS Ser1179 residue, reduced asymmetric dimethylarginine (ADMA) levels, and acting as an eNOS inhibitor by increasing

dimethylarginine dimethylaminohydrolase (DDAH) activity which ultimately result in increased nitric oxide release and vasodilation in endothelial cells. Polyphenols also modulate the nuclear factor erythroid-2-related factor - antioxidant response element (Nrf2-ARE), which positively regulates the expression of antioxidant enzymes [57, 58].

Polyphenols protect against endothelial dysfunction and inflammation through these wide molecular mechanisms, resulting in cardiovascular protection. Cocoa products have also been researched for their ability to decrease blood pressure due to their high flavonoid content [59]. Other food sources known to be rich in phenols and phenolic compounds are fruits and vegetables. Mattioli et al., (2020), stated that fruits and vegetables are rich in anthocyanins which have been reported to show anti-hypertensive effect [60]. Some studies have also documented the role of raisins, which are high in polyphenols, catechins, resveratrol, and isoflavones, in lowering blood pressure [61].

On the other hand, some researchers stated that polyphenols must be available and present at pharmacological amounts to target organs or tissues following intestinal absorption to be effective in the human body [9]. Polyphenols in food matrices are hydrolyzed and conjugated by methylation, alkylation, sulfation, and glucuronidation processes in the small intestine and liver during absorption and before reaching the systemic circulation after being consumed [62]. The remaining molecules make their way to the large intestine and colon, where they may be metabolized by the microbiota to produce other functional compounds or eliminated in the feces and urine. The interactions of phenolic compounds with food matrix constituents including proteins, fibers, and minerals, on the other hand, can reduce their bioaccessibility and oral bioavailability. In spite of these, nano-encapsulated polyphenols loaded in food-grade polymers and lipids seem safe, obtaining resistance feature in the enteric route for intestinal absorption, where muco-adhesiveness ensures enhanced uptake, resulting in high systemic levels in non-metabolized forms [63]. Nano-capsules give these drugs a more progressive release, as well as longer half-lives and cell and whole-organism permanence, enhancing their effectiveness in pre-clinical studies and allowing them to be used as an adjuvant therapy for cardiovascular disorders.

In healthy and diabetic rats, Boarescu et al. (2019), investigated the effects of nano-encapsulated curcumin on cardiac tissue in an animal model, finding that curcumin-NPs offered protection against cardiomyocyte damage, acute myocardial infarction, and post-infarction cardiac injury induced by isoprenol [64]. In another study, cherry extracts (Prunusavium L.), which are high in polyphenols (quercetin and cyanidin-3-glucoside), were encapsulated in quaternary ammonium chitosan-NPs and showed anti-inflammatory properties [65]. Nano-encapsulated polyphenols such as ferulic acid, quercetin, gallic acid, resveratrol, catechin, epicatechin, epigallocatechin, proanthocyanidin, and curcumin, as well as entire extracts from grape seeds and cherries, have been shown to have no toxicity to human cell lineages in pre-clinical studies [66].

8. Challenges and Prospects

The application of nanotechnology in medicine has a potentially tremendous impact in terms of diseases prevention, diagnosis, treatment and health promotion. The goal of using this technology is to improve treatment efficacy, lower the therapeutically effective dose, and/or lower the risk of systemic side effects. However, achieving these goals poses a number of difficulties. Biological hurdles, biocompatibility and safety challenges, large-scale manufacturing challenges, intricacy of nanomedicine patents and intellectual property, government requirements, and overall cost-effectiveness in contrast to present medicines are among them [67]. Inadequate understanding of the interaction of nanomaterials with tissues and cells, limited understanding of the biological interaction of these materials with the biological environment in the body of patients, insufficient information on the degree of accumulation of nanomedicines in target organs, tissues, and cells, and the need for the development of more specific nanopolyphenols are also important challenges associated with the biocompatibility and safety concerns of nanopolyphenols [68].

In addition, based on good manufacturing practice (GMP) standards, difficulties in large-scale production of nanopolyphenols to ensure quality

control and reproducibility in physicochemical properties on a batch-to-batch basis are potential challenges arising from their large-scale manufacture and cost-effectiveness of their production [38]. The expense of the raw ingredients used in the synthesis of nanopolyphenols further impedes their scale-up and production. To make up for the high expenses of developing and manufacturing nanomedicine products, the clinical therapeutic impact of the medications must be far superior to that of traditional therapies [38]. Finally, lack of defined regulatory rules pertaining to nanoparticulate nanomedicines in different countries poses a challenge to the prospect of nanopolyphenols.

9. Opportunities

Opportunities include: nano-encapsulation provides increased bioavailability of the drugs and also helps to develop specific targeted delivery resulting in enhanced performance of the phenolic compounds as therapeutic or preventive agents. It will likewise be beneficial for research and development (R&D) companies (biopharmaceutical and drug development companies) in their development of therapeutic agents of phenolic origin to combat chronic disease. Encapsulating the compounds in nanomaterials will help enhance the overall performance of the drugs within the human system and decrease / eliminate toxicity and side-effects.

10. Conclusions

Polyphenols are highly potent health promoting material that can be found in a wide range of leaves, stems, fruits, roots, and seeds of plant species. However, their utilization is impaired by their sensitivity to environmental factors such as heat and moisture and as such they require protection by means of encapsulation / nanoencapsulation. Based on the major findings reported and discussed in this review, the benefits of polyphenol encapsulation are enormous, ranging from enhanced anti-cancer, antidiabetic and anti-hypertensive abilities of phenolic compounds, to increased bioavailability and more progressive release of drugs in the body. Among the several other encapsulation techniques, nanoencapsulation of polyphenols offer promising results and can be achieved using polymeric, vesicular or inorganic nanocarriers. However, the variety of techniques used in the production and analysis of nano-polyphenols has a distinct impact on their physical qualities, chemical behaviour, biological interactions, analytical properties, and efficacy, placing a major limitation to their applications. It is therefore recommended that utilization of nanomaterials in the development of cost-effective nanodrug delivery systems should be augmented by a thorough understanding of polyphenols' physicochemical properties and the stabilization of nanomaterials which could enhance site-specific targeting, thus, positioning nanoencapsulated polyphenols as an invaluable tool in the prevention/management of chronic diseases.

Study Highlights

- Polyphenols are highly potent health promoting material that can be found in a wide range of plant species.
- Application of polyphenols is impaired by their sensitivity to environmental factors such as heat and moisture.
- Polyphenols require protection by means of encapsulation / nanoencapsulation.
- The benefits of polyphenol encapsulation are enhanced anti-cancer, antidiabetic and anti-hypertensive abilities of phenolic compounds, to increased bioavailability and more progressive release of drugs in the body.
- Nanoencapsulation of polyphenols offer promising results and can be achieved using polymeric, vesicular or inorganic nanocarriers.
- Utilization of nanomaterials in delivery systems should be improved by a thorough understanding of polyphenols' physicochemical properties.

Abbreviations

NPs: Nanoparticles
EE: Encapsulation efficiency
SEM: Scanning electron microscopy
R&D: Research and development
GMP: Good manufacturing practice
eNOS: Endothelial nitric oxide synthase
ADMA: Asymmetric dimethylarginine
DDAH: Dimethylarginine dimethylaminohydrolase
Nrf2-ARE: Nuclear factor erythroid-2-related factor - antioxidant response element

LDL: Low-density lipoprotein
EGCG: Epigallocatechingallate
ROS: Reactive oxygen species
STAT3: Signal transducer and activator of transcription 3
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
PEG: Poly ethylene glycol
PLA: Poly lactic acid
SLN: Solid lipid nanoparticles
AD: Alzheimer's disease
BBB: Blood–brain barrier
BACE1: β-site APP cleaving enzyme 1
Aβ42: Amyloid-beta 42

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The authors declare that they have no conflict of interest.

Ethical approval
This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution
All authors: conceptualization, preparing the first drafting, and revising the manuscript.

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