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Review

Non-Traditional Natural Stabilizers in Drug Nanosuspensions

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Abstract: Poor solubility of many drugs, with ensuing low bioavailability, is a big challenge in pharmaceutical development. Nanosuspensions have emerged as a platform approach for long-acting injectables and solid dosages that enhance drug bioavailability. Despite improvements in nanosuspension preparation methods, ensuring nanosuspension stability remains a critical issue. Conventionally, synthetic and semi-synthetic polymers and surfactants are used in nanosuspension formulations. However, no polymer or surfactant group is universally applicable to all drugs. This fact, as well as their toxicity and side effects, especially if used in excess, have sparked the interest of researchers in the search for novel, natural stabilizers. The objective of this paper is to provide a comprehensive analysis of non-traditional natural stabilizers reported in the literature published over the last decade. First, physical stability and stabilization mechanisms are briefly reviewed. Then, various classes of non-traditional natural stabilizers are introduced, with particular emphasis on their stabilization potential, safety, and pharmaceutical acceptability. Wherever data were available, their performance was compared with the traditional stabilizers. Furthermore, the benefits and limitations of using these stabilizers are examined, concluding with future prospects. This review is expected to serve as a valuable guide for researchers and formulators, offering insights into non-traditional natural stabilizers in drug nanosuspension formulations.

Keywords: drug nanoparticles; nanosuspension; natural stabilizers; aggregation; Ostwald ripening; stabilization; plant-derived; polymers; surfactants; formulation development

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1. Introduction

One of the major challenges for a wide range of drugs and drug candidates is their poorly water-soluble nature, which limits both their development and clinical applications [1]. According to the biopharmaceutical classification system (BCS), around 40% of drugs available on the market and 90% of drugs under development are classified as poorly water-soluble [2]. Conventional formulation strategies to enhance the solubility of poorly water-soluble drugs are currently limited [3]. Most widely known strategies involve salt formation and pH adjustment [4], the use of solubilizing excipients (cyclodextrins, water-soluble organic solvents, water-insoluble lipids, etc.) [5,6], emulsion-based systems [7], microemulsion-based systems [2], and solid dispersions [8]. In addition to these techniques, nanonization or nanomilling (i.e., reduction in the drug particle size to the sub-micron range) has emerged as an alternative and reliable approach, offering notable benefits [9]. Fundamentally, reducing the particle size to the nanoscale expands the drug's surface area, which subsequently leads to increased saturation solubility, dissolution rate, and enhanced bioavailability [10]. Other significant benefits of nanonization include its wide applicability across various drugs and its ease of application [11].

Nanosuspension formulation technology has emerged as a promising drug delivery approach, owing to its desirable characteristics [12]. Unlike lipid-based systems, nanosuspensions are highly efficient in formulating compounds that are not readily soluble in both water and oil [13]. Moreover, the presence of a solid-state allows for increased mass per

volume loading, which is vital for high-dose applications. This promotes effective drug delivery with higher therapeutic concentrations, resulting in maximized pharmacological effects [14]. The use of solubilizing excipients such as cyclodextrins often fails to meet these requirements [13]. Major clinical advantages include minimized toxicity due to a lack of solubilizing agents and the possibility of modifications of the drug's pharmacokinetics through controlled drug release formulations [4].

Drug nanosuspensions can be prepared by several methods broadly categorized as top-down processes (e.g., wet media milling, high-pressure homogenization, etc.) and bottom-up processes (e.g., liquid antisolvent precipitation, melt emulsification, supercritical fluid precipitation, acid-base precipitation, etc.) [15]. Combinative methods, involving sequential implementation of a bottom-up and a top-down process, can also be employed to effectively reduce the particle size [16]. Several review articles already provided an in-depth analysis of nanosuspension preparation methods: Bhakay et al. [15] systematically classified the usage frequency of several nanosuspension preparation methods over the period 2012–2017. Jadhav et al. [17] and Jacob et al. [18] explained top-down and bottom-up technologies in detail, alongside considering additional processes, such as ultrasound-assisted sonocrystallization. Pinar et al. [19] provided a well-documented analysis of drug nanosuspension preparation methods, highlighting both the benefits and drawbacks. Chin et al. [20] conducted an exceptional literature review by providing relevant patents for the associated drug nanosuspension preparation methods. For the sake of brevity, further details regarding nanosuspension preparation methods are not discussed here; readers are encouraged to see these review articles for detailed information about the processes.

Over the last few decades, substantial progress has been made in nanosuspension preparation methods; however, ensuring the physical stability of a nanosuspension continues to pose challenges [21]. As nanosuspensions are thermodynamically unstable systems, they tend to undergo aggregation, Ostwald ripening, and sedimentation, all of which result in physical instability over time during nanosuspension preparation and their storage [22]. Nanosuspension stability is of primary concern in formulation development, and a successful nanosuspension formulation entails selecting stabilizers and their concentrations judiciously [19]. Typically, synthetic (and semi-synthetic) polymers and surfactants are used in nanosuspension formulations due to their consistent quality, customizable properties, and good stability performance [23]. Hydroxypropyl methylcellulose (HPMC) is one of the most commonly employed non-ionic, semi-synthetic polymers [24]. Despite its cellulose-based origin, it is chemically modified by substituting hydroxyl groups with methyl and hydroxypropyl groups [25]. Other well-known examples of conventionally used chemically synthesized polymers and surfactants include polyvinyl alcohol (PVA) [26], polyvinyl pyrrolidone (PVP) [19], Poloxamer 188 (P-188) [17], Poloxamer 407 (P-407) [27], hydroxyl ethyl cellulose (HEC) [18], sodium dodecyl sulfate (SDS) [28], Soluplus [29], and D-α-tocopherol polyethylene glycol succinate (TGPS) [30]. In order to ensure clarity and conciseness throughout the paper, henceforth, these stabilizers will be referred to as traditional stabilizers. All stabilizers excluded from this category (i.e., natural stabilizers, colloidal superdisintegrants, charged nanoparticles) will be designated as non-traditional stabilizers.

Traditional stabilizers are widely used in formulations, and appear frequently in the majority of review papers covering nanosuspension stability. For example, Li et al. [31] compiled a vast range of publications from 2006 to 2015, focusing on the stabilization of drug nanosuspensions produced by wet media milling. They reported the drug concentration, type, and concentration of the stabilizer, as well as the average particle size after milling. Pinar et al. [19] classified stabilizers used in nanosuspension formulations by their type (i.e., polymer, surfactant) with detailed information on their structural properties. Peltonen and Hirvonen [32], presented a table highlighting the process used for preparing the nanosuspension, along with the drug and the stabilizers present in each formulation. Chin et al. [20] summarized several stabilization systems and individual stabilizers used in nanosuspensions. Wu et al. [33] conducted a comprehensive literature analysis detailing the nanosuspension preparation methods, drug delivery routes, and the stabilizers utilized

in formulations. In essence, these excellent review papers mostly offer broad information on traditional stabilizers. However, none of these review papers provided any comprehensive insights into non-traditional, natural stabilizers. Even a cursory look at these review papers suggests the need for a comprehensive review of natural stabilizers.

Unfortunately, the literature reviews focusing on non-traditional, natural stabilizers (i.e., saponins, gypenosides, alginates, food proteins, serum proteins, gums, etc.) are notably scarce. In the context of nanosuspension stability, these stabilizers are often either mentioned in a few sentences or not mentioned at all. In certain review articles, protein-based stabilizers [17,18] and food protein-based stabilizers [14,21] are touched upon briefly. Conversely, Beneke et al. [34] carried out in-depth research, primarily focusing on plant-derived polysaccharides. Nevertheless, marine and animal-sourced natural compounds, as well as lipid-based and protein-based substances, were not considered within the scope of the review. One study involving non-traditional natural stabilizers was led by Elsebay et al. [29]. This study holds significance as it covers not only the use of non-traditional natural stabilizers in formulations, but also their role in processes, such as lyophilization (freeze-drying) and spray drying. The primary limitation of their study lies in its limited focus on non-traditional natural stabilizers, which lacks analysis regarding stabilizer efficiency, optimal concentrations, comparison with traditional stabilizers, and long-term stability results.

To date, to the best of our knowledge, no review article has a sole focus on non-traditional natural stabilizers in the formulation of drug nanosuspensions. Hence, the primary objective of this paper is to perform an in-depth review of non-traditional natural stabilizers, which have been documented in the literature mainly over the last decade. Moreover, this paper provides detailed information on stability outcomes, zeta potential, and particle size, alongside formulation and process parameters, including drug type, drug concentration, stabilizer type, stabilizer concentration, and nanosuspension preparation method. The thematic coverage of this review is illustrated in Figure 1.

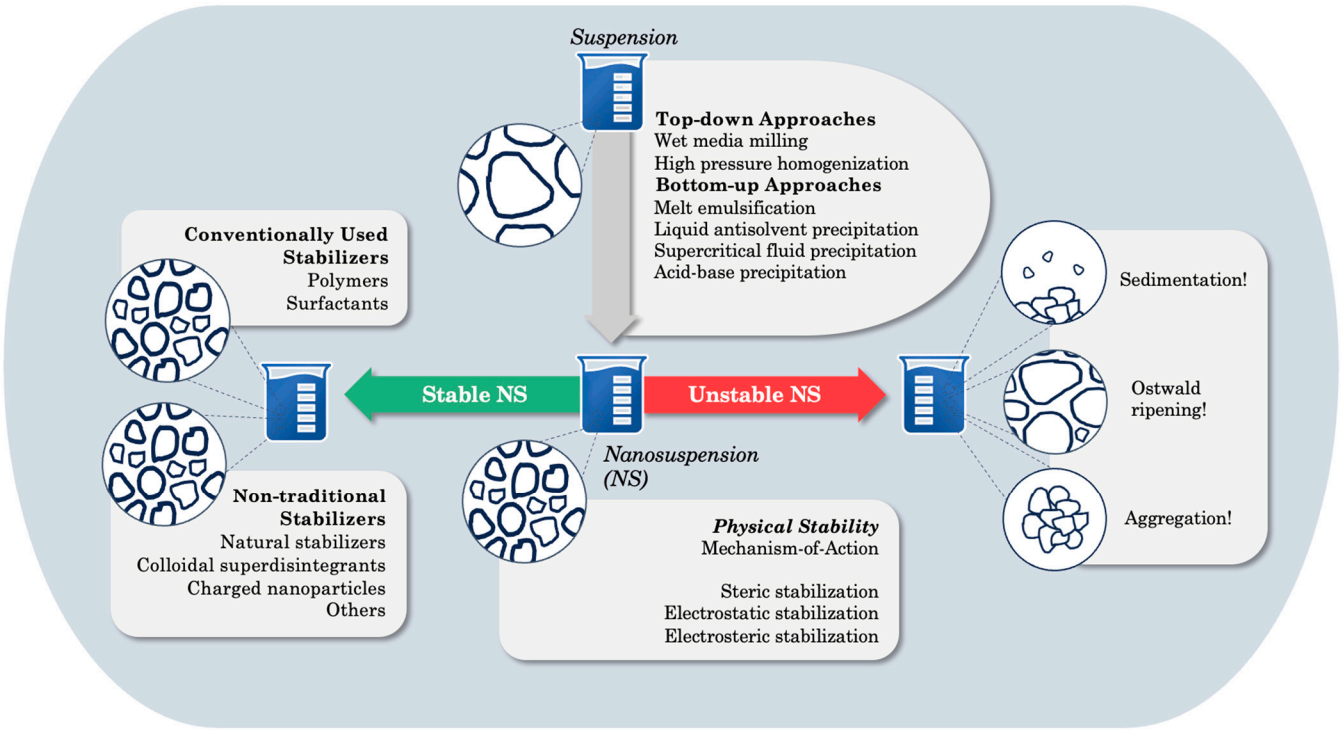

Figure 1. A thematic coverage of the review.

First, physical instability (aggregation, Ostwald ripening, etc.) and stabilization mechanisms are covered to establish a basis for assessing stabilizer effectiveness. Then, non-

traditional, natural stabilizers are examined in detail, with a focus on their stability potential, pharmaceutical safety and acceptability, and health concerns. Finally, the advantages and drawbacks associated with the use of these stabilizers are discussed, concluding with remarks on future outlooks. We anticipate this holistic approach will provide valuable insights to researchers, aiding in the development of drug nanosuspensions with non-traditional natural stabilizers.

2. Physical Instability and Stabilization Mechanisms

In this section, we review physical stability and the underlying mechanisms of stabilization. Readers seeking a more detailed understanding are referred to excellent review articles focusing solely on physical stability [32,33,35]. As previously indicated, these articles primarily focus on traditional stabilizers rather than non-traditional natural stabilizers.

Nanoparticles in suspensions are characterized by a high interfacial area, along with high interfacial free energy, which makes them thermodynamically unstable [22]. Driven by this thermodynamic instability, drug nanosuspensions aim to achieve a lower energy state by reducing their surface energy via aggregation. Ostwald ripening and sedimentation over prolonged storage are other manifestations of physical instability (see Figure 1). These issues negatively impact the fundamental characteristics of nanosuspensions, such as their small particle size and large surface area, ultimately reducing their in vivo and in vitro dissolution rates [36]. During sedimentation, drug particles tend to phase-separate, forming a dense sludge at the bottom (also known as cake). This may, in turn, make their reconstitution and redispersion through gentle agitation like simple shaking difficult [33]. Physical instability significantly reduces drug nanosuspensions' applicability in several delivery routes, including oral, parenteral, transdermal, ocular, and pulmonary applications. For example, aggregation can lead to various complications, specifically for intravenous applications. Nanosuspensions involving aggregates can cause blockages in blood capillaries and disrupt blood circulation due to bulky particles [33]. Particle size increase is a significant concern in topical and transdermal applications as well. As the skin permeation mechanism is highly particle size-dependent, an increase in drug particle size limits their ability to pass through the stratum corneum, the external barrier of the skin [37,38]. Considering these aspects, nanosuspensions lacking a relatively uniform particle size distribution are likely to exhibit reduced functional efficiency, slower dissolution rate, as well as decreased bioavailability and therapeutic outcomes.

Aggregation arises from the low surface charge of drug nanoparticles and van der Waals—hydrophobic interactions among them [15,31], while Ostwald ripening is induced by the solubility differences among particles of varying sizes [26]. Incorporating stabilizers in formulations, such as polymers and surfactants, is essential for attaining a stable nanosuspension; without them, drug nanoparticles are likely to aggregate due to elevated surface energy [17]. The primary role of a stabilizer is to adsorb on drug particles, thus preventing aggregation while mitigating Ostwald ripening [39,40]. Being hydrophilic or amphiphilic, they also reduce surface tension and enhance the wettability of the relatively hydrophobic drug particles [41]. Finally, their presence usually increases the viscosity of the base liquid (typically water), thus slowing down the Brownian motion of nanoparticles and reducing the frequency of drug nanoparticle collisions, which ultimately provides kinetic stability to the suspension.

The determination of stabilizer concentration must be guided by careful optimization. When stabilizers are used at low concentrations, they may fail to prevent aggregation; on the other hand, their excessive use can accelerate Ostwald ripening [40]. Moreover, elevated concentrations can significantly increase viscosity, potentially hindering downstream processing of nanosuspensions [15]. One must be cautious not to increase viscosity too much, which can cause viscous dampening and slowing down the nanoparticle production during nanonization [42]. In view of all these considerations, the type, concentration, and molecular weight of stabilizers should be carefully selected and optimized to achieve a physically stable nanosuspension [19,24]. Unfortunately, a predictive first-principle ap-

proach to the selection of stabilizers and their optimal concentration does not exist; such screening and optimization have always been implemented via trial and error [22]. Liu et al. [28] described stabilizer selection as a process largely dependent on empirical methods, with no established guidelines to follow. Therefore, the process of choosing the optimal stabilizer formulation is regarded as a laborious experimental task [15].

Due to concerns related to toxicity, not all stabilizers are suitable for use in pharmaceutical nanosuspensions [24]. Likewise, the utilization of improper stabilizer concentrations could result in uncontrolled aggregation and/or accelerated Ostwald ripening [31]. In this sense, the consideration of the critical micelle concentration (CMC) of surfactants is compulsory. When surfactants are used above the CMC, their molecules tend to form micelles instead of adsorbing onto particle surfaces. This leads to an increase in particle growth and aggregation due to reduced surface adsorption and solubilization of the drug inside the micelles. Readers seeking additional insights into factors affecting stability and methodologies for selecting optimal stabilizers are referred to the exceptional review article by Wang et al. [21].

Let us consider the stabilization mechanisms (see Figure 2): steric, electrostatic, and electrosteric mechanisms [32,43,44]. Steric stabilization is typically provided upon adsorption of non-ionic polymers and surfactants, such as cellulose derivatives, povidones, polysorbates, and poloxamers [31]. When particles attempt to come closer, the osmotic pressure in the overlapping steric layers works to keep them apart [45]. The electrostatic stability mechanism can be explained through the Derjaguin-Landau-Verwey-Overbeek (DLVO) theory [46]. According to this theory, the repulsive electrostatic forces and attractive van der Waals forces act on the particles. The overlap of the electrical double layer surrounding the particles generates the repulsive forces that successfully prevent aggregation and improve physical stability [33]. Electrosteric stabilization is mainly achieved when steric and electrostatic effects are both present in a nanosuspension. This can be achieved via the use of stabilizers, including both a polymeric chain and charged groups [47]. Alternatively, a non-ionic polymer can be used along with an ionic surfactant in nanosuspensions to attain electrosteric stabilization [22]. This combination facilitates synergistic stabilization effects due to the electrostatic repulsion between particles and steric hindrance provided by the polymers, as well as enhanced wetting provided by surfactants [44].

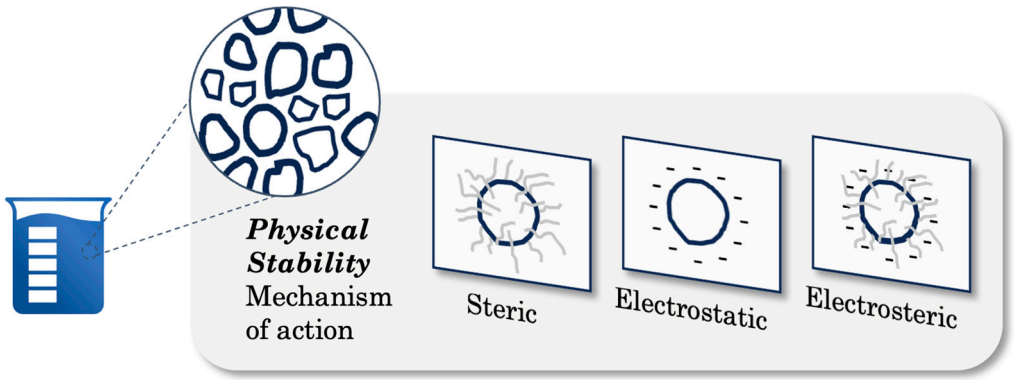

Figure 2. Steric, electrostatic, and electrosteric stabilization mechanisms.

The physical stability of drug nanosuspensions is usually assessed by measuring the particle size distribution after milling and short-term or long-term storage [35], depending on the final pharmaceutical dosage form intended (parenteral suspensions vs. solid dosages following a drying step). Zeta potential is one indicator of the physical stability of nanosuspensions. It provides an indirect measurement of diffusion layer thickness, helping to predict stability over time [48]. Typically, a minimum of $\pm$30 mV is needed for electrostatically stabilized nanosuspensions, whereas for electrosteric stabilization, at least $\pm$20 mV is considered sufficient to preserve the physical stability of a nanosuspension [49]. We caution the readers that the use of zeta potential alone may be misleading in

assessing the physical stability of drug nanosuspensions stabilized sterically or electrosterically [41], as some drug nanosuspensions with zeta potential less than 20 mV (absolute) were found to be physically stable [44,50,51]. Stabilizer adsorption isotherm for a given polymer–drug pair helps one to develop a quantitative understanding of the surface affinity of the stabilizer and drug nanoparticles [40,41]. Establishing such isotherms for several polymers may enable formulators to screen polymers rationally [52]. Finally, rheological characterization of the suspensions may also help to characterize the aggregation state in the suspensions. A drug nanosuspension with a higher extent of aggregates tends to exhibit more pronounced pseudoplastic (shear thinning) behavior [41,43]. Rheological characterization of the nanosuspensions is especially desirable as it obviates the need for diluting samples, which is a step required prior to laser diffraction, dynamic light scattering, and even scanning electron microscopy.

Although considerable progress has been made in understanding various factors influencing physical stability; further research into aggregation, Ostwald ripening, and sedimentation is needed, especially since ensuring the long-term stability of nanosuspensions continues to be a challenging area of research. Finally, a predictive first-principle-based method is still needed, however elusive it may be, to select stabilizers and set their concentrations for a given drug.

3. In-Depth Exploration of Non-Traditional Natural Stabilizers

Traditional stabilizers have been widely used in numerous nanosuspension formulations. Although they offer consistent quality with adaptable features, excessive amounts can increase toxicity and potential side effects [53]. Certain stabilizers, such as Tween 80, SDS, PEG, and PVP K-30, carry potential safety risks including chronic toxicity with long-term use [53–56]. Driven by this motivation, researchers have also searched for novel stabilizers with better stabilizing performance at lower concentrations, along with a non-toxic safety profile.

In this review, non-traditional or non-conventional stabilizers are regarded as relatively novel stabilizers in the field of nanosuspension stabilization that are not as widely used as traditional synthetic or semi-synthetic stabilizers. They are still being explored as alternative stabilizing agents, owing to their potential benefits over traditional stabilizers. These compounds include natural stabilizers, colloidal superdisintegrants, and charged nanoparticles. To maintain our focus on natural stabilizers, further details concerning colloidal superdisintegrants and charged nanoparticles are not discussed here. For additional details, readers are encouraged to consult the articles with such focus, e.g., Refs. [15,31,42,57,58].

3.1. Natural Stabilizers and Their Stabilization Potential

Natural stabilizers are chemical compounds derived from natural sources—plants, animals and marine organisms—and considered non-traditional with respect to their novel use for maintaining the stability of drug nanosuspensions in this review paper. In general, they have a wide array of potential applications in the form of binders, diluents, suspending agents, coloring agents, flavoring agents, gelling agents, and viscosity enhancers [59]. Typical examples include saponins, gums and mucilage, gypenosides, alginates, food proteins, and serum proteins. Here, we provide a comprehensive overview of selected biopolymers and biosurfactants, emphasizing their potential roles in drug nanosuspension stability. All studies referenced in this section are summarized in Table 1 to facilitate an easy comparison and analysis of data across multiple studies. In this table, we offer a thorough overview of the factors influencing nanosuspension formulation, such as stabilizer type, stabilizer concentration (%), drug type, and drug concentration (%). In addition, we intentionally included the nanosuspension preparation method in this table, as each method has an impact on the properties of the resulting nanosuspension. For example, although wet media milling and high-pressure homogenization are both widely used methods, the nanosuspensions they produce may differ in particle size and distribution [60]. As nanosuspensions

differ, natural stabilizers may exhibit varying stability performances. However, research in this area remains limited, highlighting the need for further investigation.

In Table 1, each row represents a unique nanosuspension formulation, providing specific details about stabilizer-drug composition and process details. If multiple stabilizers are used in a single formulation, their respective concentrations are presented consecutively on the same row and separated by commas. It is of utmost importance to note that the traditional polymers and surfactants are also shown in Table 1 because the cited studies compared the stabilization potential of the non-traditional natural stabilizers with that of the traditional ones. Natural stabilizers were bolded in the figure to differentiate them from traditional stabilizers. The zeta potential and average particle size values presented in Table 1 correspond to measurements obtained right after nanosuspensions were prepared. Zeta potentials are presented in millivolts (mV), and average particle sizes are displayed in nanometers (nm). The stability outcomes reported in this table provide information regarding the nanosuspension's ability to maintain stability throughout the storage period. This section also outlines details regarding sedimentation, aggregation, stabilization mechanisms, stabilization effectiveness, and formulation comparisons.

3.1.1. Glycyrrhizin

Glycyrrhizin is a type of a natural, amphiphilic saponin derived from licorice root [61]. It is additionally recognized by the name glycyrrhizic acid [62]. Essentially, it is a triterpenoid saponin that consists of two molecules of glucuronic acid, along with a single molecule of glycyrrhetinic acid [63]. Glycyrrhizin is presently attracting significant attention, with several researchers exploring its potential as a novel stabilizer for nanosuspension formulations [63]. Chen et al. [61] investigated stability and redispersibility characteristics of glycyrrhizin-stabilized andrographolide nanosuspensions (AGE-NS/GZ). They compared AGE-NS/GZ with those using traditional stabilizers like Tween 80, P-188 and TPGS. Among all nanosuspensions, AGE-NS/GZ exhibited the highest absolute zeta potential, along with the best stability performance over a one-month period. Their findings revealed that AGE-NS/GZ was able to effectively prevent the aggregation of drug nanoparticles. Another study with glycyrrhizin was conducted by Hang et al. [63]. They explored dissolution profiles and pharmacokinetics of glycyrrhizin-stabilized herpetrione nanosuspensions (HPE-NS/GZ). In order to make a comparative analysis, P407-stabilized herpetrione nanosuspensions (HPE-NS/P407) were also prepared. Both nanosuspensions were kept at 25 °C and 40 °C to assess their short-term stability. After overnight storage, both HPE-NS/GZ and HPE-NS/P407 exhibited significant particle aggregation, sedimentation, and substantial particle size increase at temperatures of 25 °C and 40 °C. Despite poor storage stability, HPE-NS/GZ displayed better hepatoprotective effects and improved bioavailability, compared to HPE-NS/P407. Overall, it appears that glycyrrhizin holds decent potential to be an effective, natural stabilizer for preparing poorly water-soluble drug nanosuspensions. It not only serves effectively as a surfactant but also holds significant potential for applications in the food, cosmetic, and pharmaceutical industries [64]. However, readers should also note that their stabilization effectiveness varies depending on the drug. For example, glycyrrhizin-stabilized andrographolide nanosuspensions were able to effectively prevent aggregation [61], whereas, aggregation and sedimentation were apparent in herpetrione nanosuspensions stabilized with glycyrrhizin [63].

Table 1. List of recent publications that made use of non-traditional natural stabilizers (**bolded**) in drug nanosuspension formulations (other stabilizers are not bolded and listed only for the sake of comparison).

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Glycyrrhizin	0.1	AGE	1	HPH	487	−43.6	Aggregation was effectively prevented.	[61]
P-188	0.1		1		550	−15.7	Compared to glycyrrhizin-stabilized nanosuspensions, they were relatively less stable.	
Tween 80	0.1		1		482	−13.4		
TPGS	0.1		1		659	−16.5		
Glycyrrhizin	N/A [h]	HPE	10 [e]	WMM	457	N/A [h]	Significant aggregation and sedimentation were observed in both nanosuspensions.	[63]
P-407	N/A [h]		10 [e]		442	N/A [h]		
Panax notoginseng	0.1	BCL	1	HPH	156	−40.1	Aggregation was effectively inhibited.	[65]
PVP-K30	0.1		1		145	−31.7	During one-month storage, NS stabilized with Tween 80 and HPMC were less stable in comparison to those stabilized with PNS and PVP-K30.	
Tween 80	0.1		1		144	−33.4		
HPMC	0.1		1		149	−29.1		
Panax notoginseng	10 [e]	BVP	1	HPH	141–160	−47.9	Panax notoginseng-stabilized nanosuspensions were relatively stable at 25 °C during one-month storage period.	[66]
RH40	10 [e]		1			−43.8		
Tea saponins	0.1	DSN	5 [f]	HPH	525 [g]	−26.0 [g]	Exhibited good stabilization even in low doses.	[67]
Glycyrrhizin	0.1		5 [f]		728 [g]	−19.0 [g]	Layered notably after one-week storage due to sedimentation.	
P-188	0.1		5 [f]		911 [g]	−14.0 [g]	Displayed a higher polydispersity index, increased particle size, and lower stability relative to tea saponins-stabilized nanosuspensions.	
PEG 6000	0.1		5 [f]		818 [g]	−12.0 [g]		
HPMC	0.1		5 [f]		674 [g]	−15.0 [g]		
PVP-K30	0.1		5 [f]		670 [g]	−13.0 [g]		
SDS	0.1		5 [f]		610 [g]	−23.0 [g]		
CMC-Na	0.1		5 [f]		905 [g]	−52.0 [g]		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Tea saponins	0.05	HDN	0.8	HPH	356 [g]	N/A [h]	Even at very low concentrations, tea saponins were able to maintain stability. Ostwald ripening was prevented. Stable nanosuspensions were obtained through steric and electrostatic effects. Effective stabilization was attributed to the good interfacial properties of tea saponins.	[54]
	0.10				255 [g]	N/A [h]		
	0.15				274 [g]	N/A [h]		
	0.20				270 [g]	N/A [h]		
	0.25				267 [g]	N/A [h]		
	0.30				264 [g]	N/A [h]		
	0.35				277 [g]	N/A [h]		
	0.40				285 [g]	N/A [h]		
	0.50				286 [g]	N/A [h]		
Glycyrrhizin	0.10				360 [g]	N/A [h]	Larger particle size and polydispersity index was observed compared to tea saponins-stabilized nanosuspensions. Overall considered, they are less stable than nanosuspensions stabilized with tea saponins.	
P-188	0.10				385 [g]	N/A [h]		
PEG 400	0.10				312 [g]	N/A [h]		
HPMC	0.10				580 [g]	N/A [h]		
PVP-K30	0.10				409 [g]	N/A [h]		
SDS	0.10				354 [g]	N/A [h]		
Gypenosides	N/A [h]	QUE	N/A [h]	HPH	462	N/A [h]	Exhibited strong stability within the pH range 6–8.	[68]

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Gypenosides	0.05	QUE	0.8	HPH	485 [g]	−27.0 [g]	Gypenosides-stabilized nanosuspensions had the narrowest size distribution (PDI < 0.1) and were highly stable. Effective stabilization was attributed to negative surface potential of these nanosuspensions. The main stabilization mechanism was hypothesized to be electrostatic repulsion. In general, all nanosuspensions, except HPMC, were able to maintain stability. Sedimentation was observed in HPMC-stabilized nanosuspensions due to presence of large particles.	[69]
	0.10				494 [g]	−28.0 [g]		
	0.15				475	−28.4		
	0.20				484 [g]	−28.3 [g]		
	0.25				496 [g]	−27.9 [g]		
	0.30				518 [g]	−25.3 [g]		
	0.40				507 [g]	−24.9 [g]		
Tea saponins	0.15				474 [g]	−27.2 [g]		
Glycyrrhizin	0.15				474 [g]	−29.7 [g]		
Soybean lecithin	0.15				463 [g]	−38.4 [g]		
P-188	0.15				465 [g]	−30.6 [g]		
SDS	0.15				471 [g]	−34.3 [g]		
Tween 80	0.15				479 [g]	−26.4 [g]		
HPMC	0.15				790 [g]	−6.23 [g]		
PVP-K30	0.15				542 [g]	−25.8 [g]		
Alginate	0.5 [e]	LOV	N/A [h]	HPH	420	−37.6	Weak stabilization occurred.	[53]
	1 [e]		N/A [h]		370	−45.9	Particle size remained stable during storage.	
	5 [e]		N/A [h]		370	−47.0		
	10 [e]		N/A [h]		466 [g]	N/A [h]	Use of high stabilizer concentrations led to higher viscosity. This resulted in weak impact force and less effective particle size reduction.	
	20 [e]		N/A [h]		494 [g]	N/A [h]		
	30 [e]		N/A [h]		605 [g]	N/A [h]		
	40 [e]		N/A [h]		650 [g]	N/A [h]		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
HPMC 2910	1 [e]	LOV	N/A [h]	HPH	600 [g]	N/A [h]	In comparison to commonly used stabilizers, alginate-stabilized nanoparticles exhibited smaller particle size with narrow distribution, even at very low concentrations. No information was provided regarding the short-term stability of nanosuspensions containing commonly used stabilizers.	[53]
	20 [e]		N/A [h]		431 [g]	N/A [h]		
PVP-K30	20 [e]		N/A [h]		370 [g]	N/A [h]		
PVP-K17	20 [e]		N/A [h]		360 [g]	N/A [h]		
PVP-K12	20 [e]		N/A [h]		390 [g]	N/A [h]		
PVA	20 [e]		N/A [h]		470 [g]	N/A [h]		
P188	20 [e]		N/A [h]		415 [g]	N/A [h]		
P127	20 [e]		N/A [h]		442 [g]	N/A [h]		
SDS	20 [e]		N/A [h]		489 [g]	N/A [h]		
Alginate	0.5	LT	1 [f]	P + US	590	−34.9	Achieved smallest particle, greatest absolute zeta potential, highest stability performance. Both steric and electrostatic effects contributed to stability performance.	[70]
	1		1 [f]		504	−41.7		
	2		1 [f]		468	−30.9		
P127	0.5		1 [f]		783	−19.6	Steric effects contributed to stability performance. The change in zeta potential with increasing concentrations was minimal.	
	1		1 [f]		617	−22.6		
	2		1 [f]		837	−20.8		
Tween 80	0.5		1 [f]		1020	−17.9		
	1		1 [f]		933	−16.2		
	2		1 [f]		987	−15.3		
HPMC	0.5		1 [f]		801	−20.9		
	1		1 [f]		794	−19.7		
	2		1 [f]		784	−21.2		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Lentinan	0.05	RG	1 [f]	P	302 [g]	N/A [h]	Lentinan generated steric hindrance on the surface of the drug, which prevented aggregation and growth of drug crystals. A weak electrostatic repulsion was observed due to low absolute zeta potential. The interaction between LNT-RG occurred through hydrogen bonding and hydrophobic forces.	[71]
	0.10		1 [f]		309 [g]	N/A [h]		
	0.15		1 [f]		239 [g]	N/A [h]		
	0.20		1 [f]		222 [g]	N/A [h]		
	0.25		1 [f]		191 [g]	N/A [h]		
	0.25		0.1		217 [g]	N/A [h]		
	0.25		0.2		249 [g]	N/A [h]		
	0.25		0.3		289 [g]	N/A [h]		
	0.25		0.4		348 [g]	N/A [h]		
	0.25		0.5		403 [g]	N/A [h]		
Soybean lecithin	0.25	DAI	0.6 [f]	P + HPH	425	−56.9	The stabilization mechanism is electrostatic. Formulations with SDS and soybean lecithin displayed good stability. Suspensions including chitosan and CMC-Na had large aggregates.	[72]
Chitosan	0.25		0.6 [f]		1600	−56.5		
CMC-Na	0.25		0.6 [f]		2300	−62.3		
SDS	0.25		0.6 [f]		460	−52.1		
P188	0.25		0.6 [f]		379	−28.0	The stabilization mechanism is steric. Formulations with steric stabilization showed smaller particle sizes compared to those with electrostatic stabilization. Among all, PEG 600 demonstrated excellent stability, due to its high (absolute) zeta potential and the lowest PDI.	
Tween 80	0.25		0.6 [f]		456	−22.0		
PEG 600	0.25		0.6 [f]		294	−24.0		
HPMC E3	0.25		0.6 [f]		363	−14.0		
HPMC E5	0.25		0.6 [f]		399	−13.0		
PVP-K30	0.25		0.6 [f]		484	−10.7		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Soybean lecithin	2	MYR	10 [f]	P + HPH	419 [g]	−41.4 [g]	All nanosuspensions were physically stable during two-week storage. Nanosuspension including soybean lecithin displayed a slight decrease in particle size.	[73]
HPMC E3	2		10 [f]		291 [g]	−17.8 [g]		
HP-β-CD	2		10 [f]		373 [g]	−30.1 [g]		
TPGS	2		10 [f]		386 [g]	−12.4 [g]		
SLS	2		10 [f]		400 [g]	−41.4 [g]		
P-188	2		10 [f]		430 [g]	−29.5 [g]		
Gum arabic	3 [f]	CUR	0.5 [f]	HPH	852	N/A [h]	Maintained stability during one-week storage.	[74]
Native SPI	0.80	IND	30 [f]	P + US	304 [g]	N/A [h]	Protein-stabilized nanosuspensions achieved consistent stability through electrosteric stabilization mechanism. Among all, denatured proteins exhibited the best stability performance in comparison to others.	[75]
Native WPI	0.80		30 [f]		153 [g]	N/A [h]		
Native β-lg	0.80		30 [f]		907 [g]	N/A [h]		
Denatured SPI	0.80		30 [f]		131 [g]	−23.7		
Denatured WPI	0.80		30 [f]		103 [g]	−30.8		
Denatured β-lg	0.80		30 [f]		210 [g]	−25.9		
PVP	0.80		30 [f]		412 [g]	N/A [h]	In general, traditional stabilizers displayed higher particle size. This is attributed to the impact of Ostwald ripening.	
HPMC	0.80		30 [f]		390 [g]	N/A [h]		
PEG 6000	0.80		30 [f]		308 [g]	N/A [h]		
EPC	0.80		30 [f]		414 [g]	N/A [h]		
Tween 80	0.80		30 [f]		402 [g]	N/A [h]		
P188	0.80		30 [f]		290 [g]	N/A [h]		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Denatured STE, denatured SPI	0.00, 0.5	RES	60 [f]	P + US	309	−24.1	The resultant mixture was unstable.	[76]
	0.10, 0.5		60 [f]		276	−24.1	The low amount of the STE addition showed stability improvement.	
	0.25, 0.5		60 [f]		196	−22.3	RES nanosuspensions displayed remarkable storage stability.	
	0.50, 0.5		60 [f]		193	−22.7		
	1.00, 0.5		60 [f]		312	−22.1	High STE concentrations resulted in decreased stability due to formation of aggregates.	
	2.00, 0.5		60 [f]		361	−20.2		
β-lg(3.4)	2 [f]	CUR	4 [f]	P + US	150	+51.0	Native β-lg stabilized nanosuspensions were stable overall.	[77]
β-lg (7.04)	2 [f]		4 [f]		153	−53.0		
β-lg (5.5)	2 [f]		4 [f]		1960	N/A [h]	Severe aggregation.	
Denatured β-lg(3.4)	2 [f]		4 [f]		142	+45.0	Authors claimed curcumin sedimentation occurred during storage.	
Denatured β-lg(7.04)	2 [f]		4 [f]		171	−51.0		
Denatured β-lg(5.5)	2 [f]		4 [f]		2740	N/A [h]	Severe aggregation.	
Denatured WPI	0.25	CAR	7 [f]	P + US	277	−23.7	All nanosuspensions exhibited less than 10% particle size increase during a three-month storage period.	[78]
P-188	0.70		2 [f]		640	−29.6		
SDS	0.50		4 [f]		225	−8.50		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Chitosan, P-407	0.3, 0.2	SPAR	0.3	P + US	459	−38.0	The individual effects of P-407 and P-188 were less effective compared to combined use.	[79]
Chitosan, P-188	0.3, 0.2		0.3		498	−40.0		
Chitosan, P-407, P-188	0.3, 0.1, 0.1		0.3		400	−39.0	After six months, the nanosuspension remained stable.	
HPMC, P-407	0.5, 0.2		0.3		137	−34.0	Nanosuspensions displayed particle size lower than 300 nm, and high entrapment efficiency (exceeding 90%), indicating good stability performance.	
HPMC, P-188	0.5, 0.2		0.3		147	−20.0		
HPMC, P-407, P-188	0.5, 0.1 0.1		0.3		85.0	−31.0		
Chitosan, HPMC, P-407	0.15, 0.25, 0.2		0.3		267	−42.0		
Chitosan, HPMC, P-188	0.15, 0.25, 0.2		0.3		285	−12.0		
Chitosan, HPMC, P-407, P-188	0.15, 0.25, 0.1, 0.1		0.3		209	−34.0		
Human serum albumin	2 [f]	PTX	3 [f]	P + US	443	N/A [h]	Due to strong adsorption on the surface of drug nanoparticles, aggregation was effectively prevented. Higher concentration of albumin led to a further reduction in particle size.	[80]
	10 [f]				400	N/A [h]		
	20 [f]				383	N/A [h]		
	40 [f]				352	N/A [h]		
	50 [f]				326	N/A [h]		
Transferrin	3 [f]				400	N/A [h]	Transferrin-stabilized formulations displayed highest stabilization performance.	
	4 [f]				304	N/A [h]		
Immunoglobulin G	3 [f]				1540	N/A [h]	Immunoglobulins promoted particle aggregation.	
	10 [f]				1820	N/A [h]		
Immunoglobulin G (4.7)	10 [f]				534	N/A [h]	Aggregation is intended to be prevented by reducing pH and adding organic osmolytes.	
Immunoglobulin G, 10% sucrose	10 [f]				360	N/A [h]		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Human serum albumin	0.3 [f]	PTX	9.2	HPH	137	−43.6	Both nanosuspensions could maintain stability.	[81]
Human serum albumin, PEG	0.3 [f]		9.1		123	−39.9		
Neem gum	0.03 [f]	ETO	0.03 [f]	P + US	89.0	N/A [h]	Neem gum-stabilized nanosuspensions displayed lower stabilization performance compared to carboxymethyl neem gum-stabilized nanosuspensions.	[82]
	0.03 [f]		0.04 [f]		104	N/A [h]		
	0.03 [f]		0.05 [f]		153	N/A [h]		
	0.04 [f]		0.03 [f]		131	N/A [h]		
	0.04 [f]		0.04 [f]		312	N/A [h]		
	0.04 [f]		0.05 [f]		333	N/A [h]		
	0.05 [f]		0.03 [f]		344	N/A [h]		
	0.05 [f]		0.04 [f]		444	N/A [h]		
	0.05 [f]		0.05 [f]		500	N/A [h]		
g-Am Neem gum	0.03 [f]		0.03 [f]		151	N/A [h]	Acrylamide grafted neem gum-stabilized nanosuspensions displayed lower Stabilization performance compared to carboxymethyl neem gum-stabilized nanosuspensions.	
	0.03 [f]		0.04 [f]		178	N/A [h]		
	0.03 [f]		0.05 [f]		403	N/A [h]		
	0.04 [f]		0.03 [f]		296	N/A [h]		
	0.04 [f]		0.04 [f]		325	N/A [h]		
	0.04 [f]		0.05 [f]		498	N/A [h]		
	0.05 [f]		0.03 [f]		365	N/A [h]		
	0.05 [f]		0.04 [f]		592	N/A [h]		
	0.05 [f]		0.05 [f]		641	N/A [h]		

Table 1. *Cont.*

Stabilizer (s) [a]	Stabilizer Concentration (%) [b]	Drug [c]	Drug Concentration (%) [b]	Process [d]	Particle Size (nm)	Zeta Potential (mV)	Stability Outcome	Ref.
Carboxymethyl Neem gum	0.03 [f]	ETO	0.03 [f]	P + US	73.0	N/A [h]	Carboxymethyl neem gum-stabilized nanosuspensions displayed smaller particle size, along with greatest stabilization performance. There was no significant change in particle size.	[82]
	0.03 [f]		0.04 [f]		84.0	N/A [h]		
	0.03 [f]		0.05 [f]		136	N/A [h]		
	0.04 [f]		0.03 [f]		177	N/A [h]		
	0.04 [f]		0.04 [f]		293	N/A [h]		
	0.04 [f]		0.05 [f]		366	N/A [h]		
	0.05 [f]		0.03 [f]		272	N/A [h]		
	0.05 [f]		0.04 [f]		464	N/A [h]		
	0.05 [f]		0.05 [f]		499	N/A [h]		
C. pulcherrima gum (1000 rpm, 1:10)	0.1	DRO	20 [f]	P	559	N/A [h]	Increasing stirrer speed, solvent-to-antisolvent ratio and stabilizer concentration contributed to a reduction in particle size. C. pulcherrima gum served as an effective stabilizer; however, it could not prevent aggregation.	[83]
	0.3		20 [f]		541	N/A [h]		
C. pulcherrima gum (1500 rpm, 1:10)	0.1		20 [f]		441	N/A [h]		
	0.3		20 [f]		416	N/A [h]		
C. pulcherrima gum (1000 rpm, 1:20)	0.1	DRO	20 [f]	P	490	N/A [h]		
	0.3		20 [f]		453	N/A [h]		
C. pulcherrima gum (1500 rpm, 1:20)	0.1		20 [f]		375	N/A [h]		
	0.3		20 [f]		346	N/A [h]		

[a] Names of the stabilizers are abbreviated as follows: SPI: soybean protein isolate; STE: stevioside; WPI: whey protein isolate; β-lg: β-lactoglobulin; HPMC: hydroxypropyl methylcellulose; P-188: poloaxomer 188; Tween 80: polysorbate; TPGS: D-alpha tocopherol acid polyethylene glycol succinate; P-407: poloxamer 407, PVP-K30: polyvinyl pyrrolidone K30; RH40: polyoxyethylene hydrogenated castor oil; SDS: sodium dodecylsulfate; PEG 6000: polyethylene glycol 6000; HP-β-CD: hydroxypropyl-β-cyclodextrin [b] with respect to suspension, w/v or w/w. [c] Names of the drugs are abbreviated as follows: RES: resveratrol; IND: indomethacin; LOV: lovastatin; RG: regorafenib; AGE: andrographolide; HPE: herpetrione; BCL: baicalein; BVP: breviscapine; DSN: diosmin; HDN: hesperidin; QUE: quercetin; LOV: lovastatin; LT: luteolin; DAI: daidzein; CUR: curcumin; MYR: myricetin; CAR: carvedilol; SPAR: sparfloxacin; ETO: etoricioxib; DRO: dronedarone; PTX: paclitaxel. [d] Nanosuspension preparation methods are abbreviated as follows: HPH: high pressure homogenization; P: precipitation; WMM: wet media milling, US: ultrasonication, [e] with respect to drug weight, [f] mg/mL. [g] Particle size data were not reported in the text; values were extracted from the figures using PlotDigitizer (3.3.9 PRO Version). [h] N/A: not available.

3.1.2. Panax Notoginseng

Panax notoginseng is a natural, non-ionic surfactant that is extracted from the roots of the plant [65]. Saponins are the primary components of panax notoginseng [84]. Other constituents include flavonoids, cyclopeptides, saccharides, sterols, amino acids, and inorganic elements. The use of panax notoginseng for various applications has gained increasing interest in recent years [85]. However, their application as a stabilizer in nanosuspension formulations is still considerably restricted. One study was carried out by Xie et al. [66], who investigated the dissolution profile and anti-platelet aggregation impact of breviscapine stabilized panax notoginseng nanosuspensions (BVP-NS/PNS). In order to make a comparative analysis, they prepared an additional nanosuspension with polyoxyethylene hydrogenated castor oil (BVP-NS/RH40). During a one-month period of storage, BVP-NS/PNS was able to maintain its stability at 25 °C. The authors attributed this success to the presence of electrostatic repulsion effects and strong adsorption onto the nanoparticles. Another study involving panax notoginseng employed baicalein as a poorly water-soluble drug [65]. Panax notoginseng-stabilized nanosuspensions exhibited improved storage stability over a one-month period, compared to nanosuspensions stabilized with Tween 80 and HPMC. This was attributed to the strong adsorption of Panax notoginseng onto the drug's surface, thereby preventing aggregation during storage.

3.1.3. Tea Saponins

Tea saponins are natural, multifunctional, non-ionic surfactants that consist of saccharides (glycosyl groups) and sapogenins (aglycons) [86]. They can be extracted from roots, leaves, flowers, and seeds of Camellia plants. There is growing interest in tea saponins for their potential advantages in taste, cost-effectiveness, and sustainability. However, research on their application in the stabilization of nanosuspensions and emulsions remains highly limited [87]. One comprehensive study was carried out by Xie et al. [67], who investigated the stability of tea saponin-stabilized diosmin nanosuspensions (DSN-NS/TS). In order to make a comparative analysis, they formulated additional nanosuspensions using traditional stabilizers (P-188, PEG 6000, HPMC, PVP-K30, SDS, etc.) and glycyrrhizin (DSN-NS/GZ). By varying drug concentration, tea saponin concentration, and process parameters, they optimized the quality of the nanosuspension. Their findings revealed that: (i) DSN-NS/TS only displayed a slight change in appearance over the one-week storage period; (ii) a noticeable layer formed in DSN-NS/GZ over time; (iii) the variation in average particle size of DSN-NS/TS remained less than 10 nm; and (iv) both the particle size and polydispersity index of DSN-NS/GZ were considerably larger than DSN-NS/TS. Another in-depth analysis that considered the stability potential of tea saponins was conducted by Long et al. [54]. They selected hesperidin as the poorly water-soluble drug and prepared nanosuspensions using tea saponins (HDN-NS/TS), along with traditional stabilizers (P-188, PEG 400, HPMC, PVP-K30, and SDS), and glycyrrhizin (HDN-NS/GZ). They altered the concentration of tea saponins, ranging from 0.05% to 0.50%, and verified the existence of an optimal concentration, even at relatively low levels. They revealed that the glycyrrhizin-stabilized nanosuspensions had significantly larger particles and a higher polydispersity index than those stabilized with tea saponins. In these two studies, tea saponins were superior to glycyrrhizin; more studies are needed to establish if this finding can be generalizable to other drugs.

3.1.4. Gypenosides

Gypenosides are a novel class of natural, non-ionic surfactants, characterized by an amphipathic structure [69]. They are essentially tetracyclic tripernoid compounds consisting of sapogenins and sugar chains. They can be extracted from Gynostemma pentaphyllum, a well-known medicinal plant widely grown in China, Malaysia, Vietnam, Thailand, Korea, Japan, India, and Bangladesh [88]. Despite their widespread recognition, the use of gypenosides as stabilizers in nanosuspension formulations remains largely unexplored. One comprehensive study was carried out by Chen et al. [69]. They investigated the

physical stability of gypenosides-stabilized quercetin nanosuspensions (QUE-NS/GY). The findings indicated that (i) the particle size of varying concentrations (0.05%–0.40%, *w*/*v*) of QUE-NS/GY measured below 520 nm, (ii) both low and high concentrations led to an increase in particle size; hence, the optimal concentration was determined to be 0.15%, (iii) absolute value of zeta potential of QUE-NS/GY ranged between 20 and 30 mV across different concentration levels. In addition, the particle size of quercetin nanosuspensions prepared with various stabilizers followed a trend in the order: HPMC > PVP-K30 > Tween 80 > tea saponins > glycyrrhizin > SDS > P-188 > soybean lecithin > gypenosides. Observations confirmed that HPMC-stabilized nanosuspension was unable to provide effective stabilization due to inadequate surface coverage and inability to provide surface charge. On the other hand, all nanosuspensions, except the one formulated with HPMC, were highly stable during a one-month storage period. The PDI value remained below 0.3, revealing that nanosuspensions maintained a uniform particle size distribution during this period. A separate study involving gypenosides was conducted by Chen et al. [68]. Using quercetin as the model drug, they evaluated the influence of pH and ionic strength on the physical stability of the nanosuspensions. Under optimal conditions, the average particle size was 462 nm, with a PDI of 0.059. The results showed that gypenosides-stabilized quercetin nanosuspensions displayed good stability within the pH range of six to eight. Given the overall findings, they concluded that gypenosides should emerge as a promising natural stabilizer for nanosuspension preparations.

3.1.5. Alginates

Alginates are natural polymers commonly used in the food industry and pharmaceutical research [89]. They are extracted from Phaeophyceae, recognized as brown seaweed [90]. Thickening, film formation, gel formation, and emulsion stabilization are some functionalities of their unique colloidal properties [91]. Elmowafy et al. [70] explored alginate-stabilized luteolin nanosuspensions (LT-NS/ALG), along with three traditional stabilizers (HPMC, P-127, and Tween 80) in varying concentrations (0.5–2.0%, *w*/*v*). Short-term stability studies were performed under ambient temperature for a one-month period. LT-NS/ALG exhibited the highest absolute zeta potential, the smallest particle size, and the best stability performance. They reported that both steric and electrostatic effects contributed to the stability performance of LT-NS/ALG, whereas the stabilization with HPMC, Pluronic F127, and Tween 80 was attributed solely to steric effects. Another study with alginates was carried out by Guan et al. [53]. They aimed to elaborate on the stabilization mechanism of alginate-stabilized lovastatin nanosuspensions (LOV-NS/ALG) with different stabilizer concentration levels (0.50–40.0%, % of drug). They additionally prepared nanosuspensions using various types of traditional stabilizers, including HPMC 2910, PVP-K30, PVP-K17, PVP-K12, PVA, P-127, P-188, SDS, etc. To assess short-term stability, nanosuspensions were stored in a closed glass vial at 4 °C and 25 °C. Their findings disclosed the following insights: (i) LOV-NS/ALG achieved a much smaller particle size with a narrower distribution, even at very low concentrations, compared to other stabilizers; (ii) when used at the lowest concentration (0.5%), alginate was inadequate to fully coat the surface of the particles; (iii) at high concentrations of alginate (10–40%), viscosity increased significantly, resulting in a reduced impact force and less effective particle size reduction; and (iv) at 1% and 5% alginate concentration levels, no significant variation in particle size was observed over a one-week period. In this study, no information was provided regarding the short-term stability of nanosuspensions involving traditional stabilizers.

3.1.6. Lentinan

Lentinan is the main active constituent of Lentinus edodes (Shiitake), which is one of the well-known edible mushrooms cultivated in China, Japan, and other Asian countries [92]. However, extraction, isolation, and purification methods for lentinan involve multiple steps that can be challenging. Despite these technical difficulties, researchers have maintained a strong interest in lentinan; it is regarded as a novel biomaterial with consider-

able potential for drug and gene delivery applications [93]. Research revealed that lentinan holds promise as a stabilizing agent. A study conducted by Suo et al. [71] explained the role of lentinan as a natural stabilizer for drug nanosuspensions. They aimed to decrease toxicity and improve the oral bioavailability of regorafenib, a poorly water-soluble drug with significant side effects, by developing lentinan-stabilized regorafenib nanosuspensions (RG-NS/LNT). Their findings revealed that lentinan created steric hindrance on the surface of regorafenib, effectively preventing the aggregation and growth of drug crystals. In contrast, the effect of electrostatic repulsion on stability was relatively weak due to low absolute zeta potential. They concluded that RG-NS/LNT not only achieved stability but also mitigated the toxicity of regorafenib on liver cells.

3.1.7. Lecithins

Lecithins are a group of phospholipids mainly used in food applications [94]. They can be extracted from both animal sources, like eggs, and plant sources, including soybeans, sunflower, rice, rapeseed, cottonseed, and canola seed [95]. Lecithin-stabilized emulsions have been shown to display excellent antioxidant activity and stability [96]. Unfortunately, we were not able to find a comprehensive study solely dedicated to the effects of lecithins on the stability of drug nanosuspensions. In other words, fully understanding the effectiveness of lecithin-stabilized nanosuspensions has remained quite complex, given factors like their varying impact across drugs, the unclear stabilization mechanism, and the lack of defined optimal concentration and processing conditions. Nevertheless, lecithins are included in several nanosuspension formulations in some studies, providing opportunities for a comparison with other stabilizers. For example, Wang et al. [72] investigated the stability of daidzein nanosuspensions prepared with various stabilizers, including non-ionic surfactants (P-188, Tween 80, etc.), non-ionic polymers (HPMC E3, PVP-K30, etc.), ionic surfactants (SDS and soybean lecithin), and ionic polymers (chitosan, CMC-Na, etc.). In this study, they evaluated the one-week physical stability of daidzein nanosuspensions at 4 °C. Nanosuspensions stabilized with ionic surfactants displayed good stability due to high absolute zeta potential. The authors stated that formulations, including ionic polymers (chitosan, CMC-Na, etc.), were also stable, although they were not in the nanometer range. Unlike what the authors claimed, we caution readers that those suspensions cannot be considered "nanosuspensions" due to the presence of large aggregates (exceeding 1000 nm). Nevertheless, the authors successfully prepared stable nanosuspensions by using a combination of two or more stabilizers. Daidzein nanosuspensions prepared with the co-stabilizers HPMC E5 and SDS proved to be the most efficient formulation. Another study was carried out by Hong et al. [73]. They examined the effect of different types of stabilizers, including HPMC E3, HP-β-CD, TPGS, SLS, P-188, and soybean lecithin, in the formulation of myricetin nanosuspensions. The smallest particle size was achieved with HPMC E3. After storage for two weeks at 4 °C, a brief stability assessment was conducted. The authors claimed that SLS had a negative influence on the stability; however, the rationale behind this claim was not provided. A slight decrease in particle size was observed for the nanosuspension stabilized with soya lecithin during storage at 4 °C. They revealed that the combination of stabilizers proved to be the most effective formulation; the combined use of HP-β-CD and TPGS produced a stable nanosuspension that remained stable for two weeks.

3.1.8. Gums

Gums are water-soluble, natural, non-starch polysaccharides [34]. They are widely used in several applications, serving as thickeners, emulsifiers, sweeteners, binders, drug release modifiers, etc. [97]. The use of natural gums is especially appealing for pharmaceutical applications, as they are cost-effective, widely available, non-toxic, and chemically modifiable [98]. Gum arabic is one of the most widely known natural gums, with its use tracing back 5000 years [99]. It is a complex, branched heteropolysaccharide that can be isolated from the Acacia senegal and Acacia seyal. Applications of gum arabic include its use

in food, confectionery, and beverage formulations [100]. It serves as an effective emulsifying agent and is widely used in the formulation of several oil-in-water food emulsions [101]. It also has the potential to serve as an effective stabilizer for nanosuspensions. Duong et al. [74] revealed the role of gum arabic as a natural polymeric surfactant in enhancing nanosuspension stability. In their study, optimal conditions involved 1:6 curcumin/gum arabic concentration ratio, 8300 rpm homogenization speed, and 40 min homogenization time. They concluded that gum Arabic-stabilized curcumin nanosuspensions maintained stability without any noticeable aggregation during one-week storage. Another study involving gums was conducted by Malviya et al. [82]. They specifically opted for neem gum (NGM), along with its two semisynthetic derivatives, acrylamide grafted neem gum (NGP-g-Am) and carboxymethylated neem gum (CMNGP) in their nanosuspension formulations. A series of experiments was designed, employing a range of concentrations of both the stabilizers (0.03–0.05 mg/mL) and the drug (0.03–0.05 mg/mL). Their study revealed that nanosuspensions stabilized with carboxymethyl neem gum exhibited much smaller particle size, along with excellent stabilization performance compared to other formulations. They further concluded that no aggregation or Ostwald ripening took place after 45 days. Furthermore, Yeole et al. [83] performed a study exploring another type of natural gum, Caesalpinia pulcherrima. They altered the solvent-to-antisolvent ratio (1:10, 1:20), the stirring speed (1000 rpm, 1500 rpm), and the gum concentration (0.1%, 0.3%, *w*/*v*) to examine their impact on the drug particle size. Their findings revealed that an increase in the three parameters led to a reduction in particle size. They asserted Caesalpinia pulcherrima gum functioned as an effective stabilizer in dronedarone nanosuspension; however, it was not able to fully prevent the formation of aggregates.

3.1.9. Food Proteins

Food proteins offer several benefits, including rich nutritional content, biocompatibility, abundant renewable sources, acceptance as natural ingredients that can be degraded by digestive enzymes, desirable functional properties, and so on [102,103]. Accordingly, they are of practical interest within the food and pharmaceutical industry. He et al. [75] formulated several indomethacin nanosuspensions with food proteins—soybean protein isolate (SPI), whey protein isolate (WPI), and β-lactoglobulin (β-lg)—as novel safe stabilizers. In order to enhance the stabilizing capability, they exposed food proteins to 105 °C for the SPI and 85 °C for WPI and β-lg. This caused the denaturation of the protein, thus exposing hidden nonpolar and disulfide bonds within the structure. Their findings emphasized that denatured protein-stabilized IND-NS had the smallest mean particle size in comparison to native protein-stabilized nanosuspensions and those with traditional stabilizers (HPMC, PVP, PEG 6000, EPC, Tween 80, and P-188). Protein-stabilized nanosuspensions achieved physical stability through combined mechanisms of steric stabilization and electrostatic repulsion. On the whole, this study emphasized the significant contribution of heat-induced denaturation to the stability enhancement of protein-based natural stabilizers. Another comprehensive study, including food proteins, was carried out by Wan et al. [76]. They investigated the combined effectiveness of denatured soy protein (SPI) and biosurfactant stevioside (STE) as novel stabilizers to formulate stable resveratrol nanosuspensions. When pure SPI was employed to stabilize RES nanosuspensions, the resultant nanosuspension was highly unstable and a notable increase in the particle size was observed over a one-month period. However, a combination of SPI (0.5 wt.%) and STE (0.25–0.5 wt.%) in nanosuspension formulations resulted in excellent physicochemical characteristics: an average particle size less than 200 nm and significant entrapment efficiency were observed. The utilization of higher STE concentrations (1–2 wt.%, exceeding its critical micelle concentration) resulted in decreased stability due to the potential formation of aggregates during storage. Their study serves as a noteworthy example of how stabilization efficiency is strongly affected by the specific concentration of the stabilizer mixture. A separate study with food proteins was conducted by Aditya et al. [77]. They prepared nanosuspensions with β-lactoglobulin in its native and denatured forms, with three different pH levels (CUR-NS/β-lg-3.4, CUR-NS/β-lg-5.5,

CUR-NS/β-lg-7.04, CUR-NS/D-β-lg-3.4, CUR-NS/D-β-lg-5.5, and CUR-NS/D-β-lg-7.04). Short-term stability studies involved one-month storage at 4 °C. Both native and denatured forms of β-lg-stabilized nanosuspensions at acidic pH (5.5) displayed significant aggregations of nanoparticles, which can be attributed to the zero protein charge at the isoelectronic point. The authors claimed that, in the denatured forms of β-lg at both acidic and basic pH levels, curcumin sedimentation was observed during one-month storage. They stated that after denaturation, curcumin might have lost its ability to bind to the sites accessible in native β-lg. The underlying reason is attributed to the conformational changes during the denaturation process. We consider this to be an interesting outcome that necessitates further investigation, since it is highly unusual for a nanosuspension to display phase separation, particularly when its reported particle size is around 100 nm. An alternate investigation focusing on food proteins was performed by Geng et al. [78]. They explored the use of WPI-stabilized carvedilol nanosuspensions, aiming to compare their effectiveness against traditional stabilizers, including P-188 and SDS. To enhance its stabilizing potential, WPI was denatured at 90 °C for 40 min. Denatured WPI-stabilized nanosuspensions exhibited the lowest particle size increase during a 3-month storage period. Based on the zeta potential results alone, Geng et al. claimed that SDS-stabilized nanosuspensions displayed the lowest stability. We caution the readers here: their data also reveal that SDS-stabilized nanosuspensions not only exhibited the smallest particle size after preparation, but also maintained their small particle size throughout storage (excellent storage stability). Furthermore, according to their measurements, the use of SDS enabled the lowest PDI of the nanosuspensions. Taking everything together, it is reasonable to conclude that the SDS-stabilized drug nanosuspension can be regarded as one of the effective formulations.

3.1.10. Chitosan

Chitosan, a continuum of progressively deacetylated chitins, is fundamentally a natural polysaccharide that provides support to various living organisms [104]. The main raw materials for chitosan production include shrimp, crabs, lobster, crayfish, and oyster [105]. Chitosan has the potential to serve as an emulsifier and emulsion stabilizer, as it forms a protective layer at oil–water interfaces and interacts with surface-active agents [106]. Given its favorable properties, its potential application as a stabilizer in drug nanosuspensions has attracted significant interest. Ambhore et al. [79] studied nanosuspensions stabilized with water-soluble chitosan (N-carboxymethyl chitosan), along with traditional stabilizers, such as HPMC E3, P-188, and P-407 in various combinations. The optimal formulation was identified to contain 0.3% (*w*/*v*) water-soluble chitosan, 0.1% (*w*/*v*) P-188, and 0.1% (*w*/*v*) P-407. After six months of storage, the optimally formulated drug nanosuspension exhibited only a 5–6% increase in particle size, suggesting that the nanosuspension maintained good stability. This study holds significance as it is among the few studies that have focused on long-term stability.

3.1.11. Serum Proteins

Serum proteins, particularly albumin (HSA) and transferrin (Trf), have gained significant attention due to their critical role as drug carriers in clinical applications [107]. The efficiency of serum proteins, particularly HSA, Trf, and immunoglobulin G (IgG), serving as potential candidates for stabilizing nanosuspensions was explored by Lu et al. [80]. The researchers evaluated their stability performance after 3-month storage at 4 °C. They observed that (i) an increasing HSA concentration led to a further reduction in particle size, (ii) Trf-stabilized formulations displayed the highest stabilization performance, and (iii) formulations, including IgG, had a tendency to aggregate, so pH adjustments were applied and organic osmolytes are incorporated into the formulation. A separate study involving HSA was led by Yin et al. [81]. Their study demonstrated that nanosuspensions formulated with HSA and PEG-modified HSA could both main-

tain stability. According to pharmacokinetic results, PEG-modified HSA nanosuspension notably improved anti-cancer efficacy.

3.1.12. Other Non-Traditional Natural Stabilizers

Other biopolymers and biosurfactants, beyond the natural compounds mentioned above, are gaining attention for their favorable properties although studies on their potential to stabilize drug nanosuspensions are relatively scarce and underdeveloped. More studies are required to confirm their suitability and effectiveness as stabilizers in nanosuspension formulations. Examples of such materials include tannic acid, inulin, pectin, and mucilage.

Tannic acid, usually extracted from oak tree galls, is a natural, safe polyphenol that has a strong potential to form hydrogen bonds with polymers and enhance solubility [108]. The findings indicate that tannic acid coating is a promising strategy to enhance the anti-schizophrenic efficacy of chrysin [109]. Drug nanoparticles coated with tannic acid were also shown to increase the mucoadhesion in the GI tract, enhancing the oral bioavailability of curcumin [110]. Unfortunately, tannic acid continues to be an unexplored material for use as the sole stabilizer in nanosuspension formulations.

Inulin is a naturally occurring polysaccharide and a prebiotic ingredient widely used in food formulations [111]. It is a water-soluble dietary fiber found in more than 36,000 plants, including garlic, onion, asparagus, and chicory [112]. Nutritional and health benefits of inulin include serving as a fat replacer, sugar replacer, and texture modifier [113]. Eerdenbrugh et al. [114] investigated the ability of inulin to preserve rapid drug dissolution after carrying out spray-drying of drug nanosuspensions. Other studies have explored the use of inulin-based polymeric surfactants for emulsion stabilization [115,116]. However, current research on their ability to stabilize drug nanosuspensions is still limited.

Pectin is usually present in large amounts within soft plant tissues, contributing to the plant's firmness and structure [117]. It is a natural, mucoadhesive polysaccharide that shows promising potential as a stabilizer for liposomal drug delivery systems [118]. Pectin is capable of forming stable emulsions similar to gum arabic, but at significantly lower concentrations [119]. However, the use of pectin in drug nanosuspensions has not been thoroughly investigated.

Mucilage is a sticky, dense hydrocolloid generated by nearly all plants and certain microorganisms [120]. It is composed of monosaccharides bonded with organic acids, and serves as a good emulsifying and suspending agent [121]. It is commonly used as a pharmaceutical additive in different dosage forms, playing roles as a stabilizing, gelling, and thickening agent [122]. Conversely, the role of mucilage as a nanosuspension stabilizer seems to remain unexplored in the pharmaceutical nanotechnology literature.

In brief, these stabilizers demonstrate considerable potential for stabilizing drug nanosuspensions. Their application in several fields, including serving as emulsifying agents and exhibiting viscosity-enhancing properties, positions them as promising candidates for use as stabilizers in nanosuspensions. Although current research remains relatively limited and underexplored, they are well-suited for use in the development of effective nanosuspension formulations. Due to their natural origin and multiple benefits, these materials can be considered non-toxic alternatives to traditional stabilizers. It has been revealed that, in recent years, the natural product market has experienced substantial growth [123]. It is likely that a shift toward the increased use of natural stabilizers in nanosuspension formulations will be observed in the following years.

3.2. Pharmaceutical Safety, Acceptability and Health Concerns

An important consideration alongside stability is the safety profile of stabilizers. It has been established that most research efforts primarily concentrate on physical stabilization aspects; however, studies on toxicological impacts remain limited [14]. For practical applications, a stabilizer's safety profile is important to ensure that it does not cause any toxicity or adverse effects. Below, we emphasized key aspects related to pharmaceutical safety, acceptability, and health concerns of the natural stabilizers.

Glycyrrhizin is frequently used in traditional Chinese herbal medicines as a natural resource [61]. With a sweetness level 50 times greater than sucrose [124], it is of considerable interest in the food industry. El-lahot et al. [125] investigated glycyrrhizin as a safe alternative to sucrose for sweetening toffee and cake preparations. Their study revealed that glycyrrhizin-treated rats experienced a notable decrease in their triglyceride values in comparison to control groups. Glycyrrhizin-stabilized herpetrione nanosuspensions have also been shown to be effective in lowering serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [63]. According to the European Food Safety Authority (EFSA), a daily intake of glycyrrhizin of 100 mg is regarded as safe [126,127]. On the other hand, it has been reported that even smaller doses can cause adverse effects; therefore, several studies proposed using significantly lower amounts, i.e., 0.015–0.229 mg/kg body weight/day [128].

Panax notoginseng is a widely recognized medicinal herb and finds extensive application across the food industry, particularly in China [65]. It ranks first in sales volume across the entire Chinese patent medicine market, with its market size exceeding 10 billion yuan [85]. Given its extensive application in clinical treatments, only a few studies have investigated its potential toxic effects [84]. Excessive doses of panax notoginseng may result in adverse effects, including nausea, vomiting, and nosebleeds. In light of these findings, certain individuals, such as pregnant women, are advised to use this medicinal herb with caution.

Tea saponins have been reported to be non-irritating and easily biodegradable agricultural by-products [67,87]. When fed to *H. armigera* larvae, they caused significant mortality within one week [129]. Given their toxic effects on *H. armigera* larvae, they are recommended for use as natural-derived insecticides and biopesticides. On the other hand, as tea saponins are deemed safe for human consumption, they are widely used as emulsion stabilizers in beer and soft drinks [54]. They have been widely studied within the food industry as well, with research confirming their safety for use as a food preservative with anti-yeast activity [130]. The use of tea saponins is expected to become a prominent subject of interest in the near future, yet there are noteworthy challenges to be addressed, such as (i) the need for further improvement in the extraction and purification technology, (ii) limited scale-up applicability, and (iii) influenced material properties by changes in concentration, pH and temperature of the nanosuspension [131]. Hence, to ensure safety and achieve the desired properties, further research into the optimal conditions is required.

Gypenosides have a broad range of applications for the treatment of various diseases including diabetes, hypertension, obesity, and hepatosteatosis [132]. Due to their role as bioactive compounds with multiple pharmacological effects, it is indeed challenging to categorize them as pharmaceutical excipients. On the other hand, when used in small concentrations, they are well-suited for applications as natural emulsifiers for oil-in-water nanoemulsions [133]. In addition, readers should note that the therapeutic effects of gypenosides are generally observed when they were intended to be used as an active ingredient at very high doses (see, e.g., [88]). Such effects are not expected to be significant when they are used at relatively low concentrations, typically 1–10% (with respect to the drug) in drug nanosuspensions. Another key point is that the toxicity of these chemicals needs to be further studied when they are used as nanosuspension stabilizers.

Alginates are linear unbranched polysaccharides known for their biocompatible and biodegradable characteristics [89]. They find significant applications within the food industry, where they are commonly used for coating fruits and vegetables to avoid microbial and viral contamination [134]. Their potential to encapsulate natural substances has made them valuable for drug coating and delivery applications as well. Accordingly, the use of alginates for drug delivery across oral, parenteral, pulmonary, and transdermal routes has been widely studied [135]. Although alginates are typically regarded as non-toxic polymers, several impurities, including heavy metals, proteins, and endotoxins, can still be present after extraction from natural sources [90]. These impurities must be controlled for compliance with pharmaceutical regulations, particularly for parenteral administration.

Taking everything into account, alginate-based drug delivery systems are promising and have great potential for future applications in the field of pharmaceutical nanotechnology. Readers seeking guidance for further research on alginate polymers may find valuable insights in the comprehensive work of Hariyadi et al. [135].

Lentinan is essentially a natural, biocompatible, multifunctional polysaccharide that has contributed to the development of various formulations aimed at treating breast cancer, lung cancer, colorectal cancer, myeloid leukemia etc. [93].

Lecithin stands as the leading natural emulsifier in the food industry [95]. It serves not only as an authorized food additive, but it is also used in cosmetics and lubricants as well. Soybean lecithin has become the main commercial source of food-grade lecithin, appreciated for its low cost and suitability for vegan applications. According to the EFSA, the use of lecithin poses no safety concerns [136]. They are commonly used in chocolate and margarine manufacturing, along with nutritional beverages and supplements [137]. In essence, they have broad applicability across various fields, providing substantial health benefits and a strong capacity to stabilize emulsified products [138].

Gums, in general, are highly tolerated by the human body owing to their simple breakdown into monosaccharides by colonic bacteria [97]. Gum arabic, as one of the most widely known gums, has been used to treat chronic kidney diseases in Middle Eastern countries [99]. Due to its safety profile, natural origin, biodegradability, and biocompatibility, it is widely used in food, pharmaceuticals, and several other industries [139]. Findings suggest that gum arabic may support dental remineralization and exhibit antimicrobial activity, indicating potential dentistry applications [140]. Neem gum, or Azadirachta indica gum, is also classified among natural gums [141]. It is a novel, natural compound with potential applications in drug delivery and gene delivery applications. It is recognized as a non-toxic, biocompatible, water-soluble polysaccharide with an abundance of functional groups [142]. Caesalpinia Pulcherrima gum is another member of the natural gum family. The seeds within pods contain gum that can be used in food applications as a texture modifier and dietary fiber source [143,144].

Food proteins generally possess a non-toxic safety profile and are suitable for human consumption [77]. They not only offer nutritional benefits but also act as a potential resource to enhance the body's natural defense against pathogens [145]. Ovotransferrin, α-lactalbumin, and β-lactoglobulin are examples of food proteins known for their antimicrobial properties. Other well-known food proteins include rice protein, soybean protein, pea protein, whey protein, milk (cow, sheep, and goat), casein, albumin, oat, and so on [146]. Compared to other food proteins, whey proteins have an exceptionally high concentration of branched-chain amino acids, particularly L-leucine [147]. This is significant in the sense that leucine can engage with the insulin pathway, promote protein synthesis, and help preserve muscle protein during limited energy intake periods [148]. On the contrary, a notable health concern associated with food proteins is their potential to cause allergic reactions. Commonly recognized foods linked to such allergies include eggs, fish, shellfish, milk, peanuts, soy, tree nuts, wheat, etc. [149].

Chitosan is a natural biodegradable biopolymer that holds potential as a safe, pharmaceutical excipient [150]. When combined with a monophosphoryl lipid, chitosan can potentially stimulate a robust immune response [151].

Serum proteins, such as Trf, HSA, and low-density lipoprotein (LDL), hold promise for the targeted delivery of anti-cancer agents [152]. Among all proteins, HSA emerges as a versatile protein carrier since it is highly stable under varying pH and temperature [153]. It is frequently used in clinical applications to treat multiple cardiovascular, acute, and chronic diseases.

Tannic acid is a promising natural antioxidant that has extensive potential applications in pharmaceuticals, biomaterials, and drug delivery strategies. When used at certain doses, it can act as an antibiotic against bacteria and reduce inflammation [108].

Inulin is accepted in several countries as a food ingredient, allowing for unrestricted use in food formulations; however, higher doses may result in intestinal discomfort [154].

Studies have also confirmed that inulin has the potential to boost the immune system of the body [155].

Pectin is globally accepted as a safe natural dietary fiber, offering several health benefits, including anti-inflammatory characteristics, cholesterol and fat reduction, immune system support, and cough suppression [156]. It is also an effective vehicle for anti-cancer drug delivery applications, given its modifiable functional groups and desirable physicochemical properties [157].

Mucilage has proven to be a natural polysaccharide frequently used in biomedical and food applications [158]. The use of mucilage in the food industry spans a variety of products, including bakery products, meat emulsions, fermented dairy products, and ice cream. Within biomedical applications, mucilage is commonly used in tissue regeneration, drug delivery systems, and wound dressings. Valuable features of mucilage include, improved patient tolerance, minimal side effects, non-allergenic nature, skin-friendly quality, and low production costs [120]. Although mucilage is regarded as a promising material utilized across multiple applications, its properties are still not fully optimized.

3.3. Other Limitations, Challenges, and Advantages

Non-traditional natural stabilizers are generally considered safe materials. Owing to their biocompatible characteristics, they have been used in pharmaceuticals, food, and cosmetic products where safety is a priority. On the other hand, their toxicity must be examined to confirm their safety for specific applications and intended delivery routes, as higher doses may lead to potential health risks, allergic reactions, or undesirable side effects. One benefit of non-traditional, natural stabilizers is their good–excellent stability performance in drug nanosuspensions. Various studies have demonstrated that, with few exceptions, natural stabilizers can outperform traditional stabilizers in terms of stability [61,70,75,78,79]. Similarly to traditional stabilizers, they can be effective for multiple drugs. For example, tea saponins can successfully maintain nanosuspension stability across two different drugs, diosmin and hesperidin [54,67]. Natural stabilizers also have the potential to stabilize nanosuspensions without the need for co-stabilizers [67]. Also, combination strategies with other natural compounds, like the use of soybean protein isolate with biosurfactant stevioside, can improve the overall stability as well [76]. This allows for fine-tuning of formulations to optimize nanosuspension stability. In addition, natural stabilizers exhibit eco-friendly features, including biodegradability and sustainability. Naturally degrading stabilizers can aid in reducing the risk of pollution, accumulation, and long-term environmental toxicity. Additionally, they avoid reliance on fossil fuels or non-renewable chemicals, as they are typically extracted from renewable sources. Multi-applicability is another feature of natural stabilizers. They can be used across a wide range of applications, including food, beverage, cosmetic, personal care, agriculture, biomedical, and pharmaceutical industries. Furthermore, they are generally highly effective even in low concentrations [67], which makes them an economical choice in various applications. Traditional and cultural acceptance is another advantage of using natural stabilizers. As most of these compounds have been widely used for centuries in various countries, they can be more readily accepted by patients and customers. These benefits make natural stabilizers a valuable choice across various pharmaceutical applications.

One major challenge related to non-traditional, natural stabilizers is variability. Variability can arise from either source-to-source differences or lot-to-lot inconsistencies [159]. The former is alternatively referred to as intersource variability, while the latter is known as interlot variability. Both intersource variability and interlot variability can exist in natural stabilizers. Due to their dependence on natural sources, stabilizers cultivated in various regions may exhibit significant variations in their stability characteristics. In addition, variability can be influenced by environmental factors (rainfall, temperature differences, etc.) as well as manufacturing processes (drying, purification, extraction techniques, etc.) [123]. Harvest seasons or storage methods can contribute to variability as well. For example, chitosan-based formulations are highly susceptible to environmental factors and processing

conditions [160]. Also, different manufacturing applications and diverse sources of chitosan result in notable differences in the quality and characteristics of the final product. Likewise, pectin encounters notable difficulties for its standardization. Since pectin is a complex mixture of polysaccharides, rather than a single compound, its variability can be easily influenced by factors like extraction process, source, and degree of esterification [156]. Mucilage also experiences variability issues due to its uncontrolled hydration behavior. It has a strong affinity for water; hence, maintaining a consistent level of moisture within mucilage-based products is a concern in applications where uniform performance and long-term stability are essential. All these considerations highlight the necessity of implementing proper standardization procedures to reduce variability and ensure consistency. These aspects are closely related to reproducibility and scalability-related challenges. Without proper standardization, additional steps, like reprocessing, can be required, which could lead to an inefficient scaling-up process. Likewise, a lack of reproducibility may result in inconsistent products, resulting in higher costs and extended production timelines.

Another possible limitation of using some non-traditional natural compounds as stabilizers in nanosuspensions is their additional processing needs, such as carboxymethylation, PEGylation, heat treatment, and pH adjustments. For instance, chitosan is only soluble in acidic conditions, which limits its use in drug delivery applications [79]. To address this challenge, the carboxylation process is implemented to produce water-soluble grade chitosan for its use in nanosuspension formulations. In addition, pH-dependent solubility is one of the key challenges for gums. Modification applications to tackle this problem include derivatization of functional groups, grafting with polymers, cross-linking with ions, etc. [97]. Food proteins also undergo additional processing steps. In several studies, heat-denaturation was applied to enhance the effect of stabilization [75,77]. At this point, it becomes essential to evaluate whether natural compounds, after undergoing processing, can still be classified as "natural stabilizers" in formulation applications. This highlights a significant labeling concern that motivated us to explore the definition of "natural". According to the Food Safety and Inspection Service (FSIS) [161], minimal processing allows for a product to be classified as natural, as long as the process does not fundamentally change the compound. The U.S. Food and Drug Administration (FDA) [162] uses this term to indicate that no artificial or synthetic ingredients have been included in or added to a product that would not be ordinarily present in that product. However, the FDA definition lacks clear guidelines regarding how various food processing and manufacturing methods (i.e., thermal technologies, pasteurization, or irradiation) are treated under this definition. In accordance with these definitions, it is reasonable to claim that highly processed or chemically modified natural stabilizers will not meet the "natural" designation. These examples include carboxymethyl chitosan, pegylated chitosan, and acrylamide grafted neem gum.

4. Conclusions

This review paper offers an in-depth analysis of non-traditional natural stabilizers used in drug nanosuspensions. It provides (1) a perspective by linking stability outcomes, zeta potential, and average particle size, with formulation parameters, including drug type, concentration, stabilizer characteristics, and preparation method; (2) a nuanced understanding of how novel, natural materials exhibit unique properties that may contribute valuable functionality across different nanosuspension formulations; (3) emerging trends and gaps in the selection of natural stabilizers; and (4) unexplored aspects for future research. Based on our analysis regarding literature studies, particularly focusing on the last decade, natural stabilizers can provide better stability performance compared to traditional stabilizers, especially non-ionic polymers; a single drug can be stabilized by more than one type of natural stabilizer, either individually or in combination with other natural stabilizers; the stabilization performance of natural stabilizers differ depending on the type of the drug; and varying the concentration of a natural stabilizer result in different stability outcomes. Thus, it is highly important to determine the optimal concentration of

the natural stabilizer to achieve a physically stable nanosuspension. Certainly, there may be instances in which they are unable to effectively prevent aggregation, maintain the stability of nanosuspensions, or perform better than traditional stabilizers despite optimization. Nonetheless, natural stabilizers in drug nanosuspension formulations are promising.

Numerous substances in nature await further exploration, having the potential to be used as natural stabilizers. Ongoing research is necessary to ensure that natural stabilizers comply with safety and regulatory standards. In this concept, addressing intersource and interlot variabilities is critical to ensure that natural stabilizers are consistently safe, effective, and suitable for industrial and clinical applications. An additional potential direction for future research involves the investigation of the long-term stability of natural stabilizers. Since the majority of current studies have focused on short-term stability, and are thus often limited to a couple of weeks, there is a need for more research exploring extended periods to provide a comprehensive understanding of formulations. We believe our study will not only serve as a valuable guide for researchers but also encourage the adoption of novel, natural stabilizers in nanosuspension formulations. Given that natural stabilizers are newly emerging, they require additional toxicity studies and optimization to reach their full potential in drug nanosuspension applications.

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