Medical and pharmacokinetic effects of nanopolyphenols: A systematic review of clinical trials

Theresa F. Rambaran1 | Anna Nordström1,2

1 Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden
2 School of Sport Sciences, UiT Arctic University of Norway, Tromsø, Norway

Abstract

A significant percentage of the population has been turning to herbal remedies either as a sole treatment option or in combination with other drugs. Efforts to increase the production of therapeutic remedies from these scaffolds have therefore amplified. A fundamental aim when developing new drugs is to develop drugs that have virtually no or less adverse effects than those currently available while being efficacious. Several approaches have been undertaken to use nanotechnology to develop nanoencapsulated polyphenols for use in therapeutics in an attempt to improve their physicochemical properties, bioavailability, and efficacy. This review covers the types of nanopolyphenols that have been evaluated in clinical trials against various medical conditions and their outcomes. Medical conditions covered include cardiometabolic diseases, inflammatory diseases, and cancer and in almost all instances the nanoencapsulated polyphenol produced a positive outcome. Similar outcomes were also reported for pharmacokinetic analyses. The review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews as CRD42020172642.

KEYWORDS

clinical trial, nanoencapsulation, nanomedicine, nanopolyphenols, pharmacokinetic effect

1 | INTRODUCTION

The word "drug" is derived from the Dutch word droog (via the French word drogue) which means "dried plant." The use of plants and their extracts as active ingredients for therapeutic applications is the practice of herbal medicine and dates as far back as at least 5000 years to the Sumerians (Falodun, 2010). Notwithstanding their historically acclaimed efficacy, herbal medicines have been challenged by some practitioners of mainstream/western medicine. In recent years, however, there has been a resurgence of interest in the area due to the side effects of pharmaceuticals and the quest to find new drug candidates that can be used for the prevention and treatment of life-threatening and/or debilitating diseases (Pan et al., 2014; Pan et al., 2010).

Various plants and their parts can be used in herbal therapy and the resulting phytochemicals and their biological effects can be vast. The mere consumption of these biologically active principles, however, does not directly correlate to health beneficial effects since this is determined by their pharmacokinetic properties (Rambaran, Bergman, Nordström, & Nordström, 2020). In addition to this, efficacy is also dependent on other factors, including dosage, food matrix, and stability of the compound during metabolism (Shahidi, Ramakrishnan, & Oh, 2019). Absorption can occur via passive, active, or facilitated transport mechanisms in the body and is required for the end products of digestion to enter blood or lymph. As a result of this, a critical parameter that influences the therapeutic efficacy of a drug is its bioavailability.
Plant polyphenols, which can be classified as phenolic acids, flavonoids, or nonflavonoids, are believed to have numerous health benefits (Rambaran, 2020). There are, however, several factors that affect their bioavailability. Among these are food processing or other food-related factors, such as storage, interaction of the polyphenol with other food components, or most importantly (in the context of this review), polyphenol-related factors, such as chemical structure and particle size (Bohn, 2014; D’Archivio, Filesî, Varî, Scassacchio, & Masella, 2010). The biological activity—and by extension the application of polyphenols—is also inhibited by their rapid elimination, low water-solubility, and instability at low pH (Rambaran, 2020). These limitations have resulted in an upsurge in attempts to utilize nanotechnology to counter the challenges. One of the results of these efforts is the nanoencapsulation of polyphenols to prepare nanopolyphenols. The nanoencapsulation techniques available include physical, chemical, and physicochemical methods, such as mechanical milling, in-situ polymerization, and coacervation, respectively, among others (Rambaran, 2020). These techniques can follow a top-down or bottom-up approach and have generally been reported to result in materials with improved pharmacokinetic properties (Farokhzad & Langer, 2009). Nanopolyphenols are, therefore, expected to have superior properties to their nonencapsulated counterparts due to improvements in properties, including morphology, particle size, solubility, and surface characteristics. These improvements can then allow for targeted drug delivery and sustained drug release (Rambaran, 2020).

In order to assess recent efforts to improve the fate of polyphenols through the application of nanotechnology, a systematic review of clinical trials that assess the therapeutic or pharmacokinetic potential of nanopolyphenols is presented.

## 2 | METHODOLOGY

A systematic review was performed using PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science from inception until March 2020. The search strategy used to retrieve literature from PubMed was: ((polyphenol OR flavonoid OR myricetin OR “flavan-3-ol” OR biflavonoids OR catechin OR flavanone OR flavone OR phenols OR flavonol OR isoflavone OR proanthocyanidin OR tannins OR resveratrol OR “isoquinoline flavonoid” OR flavanolignan OR stilbene OR “phenolic acid” OR anthocyanin OR anthocyanidin OR extract OR anthraquinone OR “hydroxybenzoic acid” OR “caffeic acid” OR nanopolyphenol) AND (nano OR nanoparticle OR nanocapsule OR nanoconjugate OR nanocolloid OR nanomicelle OR nanoemulsion OR nanocomposite OR nanostructure OR nanoencapsulate OR nano-encapsulation) AND (randomized OR randomised OR “clinical trial” OR “randomized clinical trial” OR randomization OR randomisation OR RCT)). The reference lists of retrieved systematic reviews and included studies were also hand searched to find additional articles. Retrieved articles were merged in EndNote (version X9, for Windows, Clarivate Analytics, Philadelphia, PA, USA) and Rayyan software (HBKU Research Complex, Doha, Qatar) to enable the review process (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). All retrieved articles were read independently by two reviewers and disagreements were discussed and resolved by consensus.

The review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020172642). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used to conduct the review (Moher et al., 2015). The titles, abstracts, and full texts of published randomized trials were screened to determine if they met the following inclusion criteria: (1) participants of any age, health status, and from any geographic location could be included in the study, (2) the intervention included nanopolyphenols which could be prepared from pure or crude polyphenols and could be administered in various forms (e.g., capsule or gel) via various routes (e.g., intravenous or oral) with no limitations on dosage or study duration, (3) a pharmacokinetic effect or medical condition was assessed postadministration of nanopolyphenol, (4) the study design was parallel-group or crossover RCT, and (5) the paper was published in English. Studies were excluded if participants engaged in strenuous exercise and if a size greater than 1000 nm was reported for the nanopolyphenol.

### 2.1 | Data extraction and risk of bias

The following data from eligible studies were extracted: general study characteristics (first author, year of publication, country, type of polyphenol and the form in which it was administered, type of nanocarrier and its particle size, nanopolyphenol dosage, the comparator or control used in the study, and study duration), characteristics of the participants (number of participants, percentage of male participants, mean age or age range of participants, and the condition or parameter assessed within the study population), and primary outcome results.

Risk of bias in the included studies was assessed using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and was done in duplicate (Covidence). The methodological quality of the studies was assessed to determine if their risk of bias was low, high, or unclear as it relates to the methods used for sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, and to determine the chances of incomplete outcome data and selective outcome reporting.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Study characteristics

The study selection process is shown in Figure 1. The initial search yielded 727 publications, and 4 articles were identified by hand search. Removal of duplicates resulted in a total of 578 articles. The title and abstract of these were screened and this resulted in 65 articles for full
text review. An additional 36 articles were excluded thereby leaving 29 articles to be included in the qualitative synthesis.

Study characteristics of the 29 included articles are outlined in Table 1. Studies were published between the years 2011 and 2020 with more than 75% being published in Iran (n = 22). The remaining studies were published in Thailand (n = 3), Italy (n = 2), Japan (n = 1), and Spain (n = 1). The nanoencapsulated polyphenols used in the studies included quercetin (n = 1), gingerol from ginger (n = 1), α-mangostin from mangosteen (n = 2), polyphenols found in grapes (n = 1), and curcumin (n = 24). All curcumin nanopolyphenols were administered in the form of capsules with the exception of one that was administered in liquid form. The quercetin, gingerol, and α-mangostin nanopolyphenols were all administered in the form of gels, while the polyphenol-rich grape extract was administered as enriched red wine. Nanomicelles were the main nanocarrier used (n = 15) followed by polymeric nanoparticles (n = 4), nanostructured lipid carriers (NLC, n = 1), nanocrystals (n = 1), and a nanohydrogel (n = 1). The remaining seven studies did not reveal the type of nanocarrier used. In cases where the information was available, the particle size ranged from 10 to 820 nm and dosage for oral administration from 80 to 3000 mg/day. The duration of the nanopolyphenol intervention ranged from 1 to 365 days and a range of 7 to 118 participants were included in each study with a mixture of males and females in most study. Participants were 15–80 years old with a diverse range of medical conditions.

3.2 Data quality

The risk of bias assessment for the 29 included studies is summarized graphically in Figure 2. The domains assessed included random sequence generation and allocation concealment (which both assess selection bias), blinding of participants and personnel (which evaluates performance bias), blinding of outcome assessors (a measure of detection bias), incomplete outcome data (which measures attrition bias), and selective reporting (which assesses reporting bias). There was a mixture of low, unclear, and high risks of bias for all parameters with the exception of attrition bias which had only low (greater than 75%) and unclear risks. Additionally, detection bias was the only factor with less than 50% of its associated risks being ranked low. Overall, this indicates that while the risk of incomplete outcome data being reported for participants was very low across the studies, the risk of outcomes being affected by knowledge of the intervention received was of concern. No other biases were found within the studies.

3.3 The efficacy of nanopolyphenols in clinical trials

The impact of nanopolyphenols of various origin on several medical and pharmacokinetic parameters was evaluated for the included
| Author, year | Country | Polyphenol (form) | Nanocarrier (particle size, nm) | Quantity administered (mg/day)/% | n (% males) | Agea | Trial duration (days) | Comparator/ control | Condition/ parameter assessed | Outcome |
|-------------|---------|-------------------|-------------------------------|---------------------------------|-------------|------|----------------------|-----------------|-----------------------------|---------|
| (Gallelli et al., 2020) | Italy | Quercetin (gel) | Nanohydrogel (−) | 0.2% | 56 (50) | 62 | 365 | Hyaluronic acid (0.2%) | | Diabetic foot ulcer | Nanodrug and oleic acid significantly reduced wound healing time and did not cause topical or systemic side effects |
| (Asadi et al., 2019) | Iran | Curcumin (capsule) | – | 80 | 72 (13) | 30–60 | 56 | Placebo capsule | Diabetic polyneuropathy | ↓ Mean score of depression and anxiety in the nanocurcumin group Changes in stress score were not statistically significant |
| (Asadi, Gholami, Siassi, Qorbani et al., 2019) | Iran | Curcumin (capsule) | Nanomicelle (10) | 70 (44) | 59 | 84 | Placebo capsule | Diabetes mellitus (Type 2) | ↓ HbA1c, FBS, total score of neuropathy, and total reflex score |
| (Rahimi et al., 2016) | Iran | Curcumin (capsule) | Nanomicelle (10) | 80 | 70 (44) | 59 | 84 | Placebo capsule | Diabetes mellitus (Type 2) | ↓ HbA1c, FBS, TG, and BMI Longitudinal changes in FBS, HbA1c, eAG, TG, TC, LDL-C, HDL-C, and BMI before and after study |
| (Jazayeri-Tehrani et al., 2019) | Iran | Curcumin (capsule) | Nanomicelle (−) | 80 | 84 (55) | 42 | 84 | Placebo capsule | Overweight and obesity with NAFLD | Significantly increased HDL, QUICKI, and nesfatin Decreased fatty liver degree, liver transaminases, WC, FBS, BMI, HbA1c, TG, TC, LDL, HOME-IR, TNF-α, hs-CRP, and IL-6 No impact on BMI, BC, or BP |
| (Dastani et al., 2019) | Iran | Curcumin (capsule) | Nanomicelle (10) | 80 | 40 (42) | 61 | 5 | Placebo capsule | Arrhythmia and heart failure in patients with unstable angina | No significant differences between atrial and ventricular arrhythmias and other echocardiographic parameters |
| (Aslanabadi et al., 2019) | Iran | Curcumin (capsule) | Nanomicelle (−) | 480 | 110 (60) | 18–80 | 273 | Treatment was nanocurcumin plus standard treatment, control was standard treatment only | Myocardial injury | Nonsignificant ↑ in CK-MB in nanocurcumin group No significant difference in troponin I levels at 8 and 24 h after PCI between groups |
| (Dolati, Aghebati-Maleki et al., 2018) | Iran | Curcumin (capsule) | Nanomicelle (10) | 80 | 41 (39) | 28–51 | 180 | Placebo capsule | Multiple sclerosis | Restored the expression pattern of dysregulated miRNAs |
| (Dolati, Ahmadi, Aghebati-Maleki et al., 2018) | Iran | Curcumin (capsule) | Nanomicelle (10) | 80 | 41 (39) | 28–51 | 180 | Placebo capsule | Multiple sclerosis | Significantly decreased mRNA expression levels of miR-145, miR-132, miR-16, STAT1, NF-κB, AP-1, IL-1β, IL-6, IFN-γ, TNF-α, and selected chemokines Significantly increased expression levels of miRNAs targets; sirtuin-1, FoxP3, and PDCD1 |

(Continues)
| Author, year          | Country | Polyphenol (form) | Nanocarrier (particle size, nm) | Quantity administered (mg/day)/% | n (% males) | Age<sup>a</sup> | Trial duration (days) | Comparator/ control | Condition/ parameter assessed | Outcome |
|-----------------------|---------|-------------------|---------------------------------|---------------------------------|-------------|--------------|--------------------|---------------------|-------------------------------|---------|
| (Dolati, Ahmadi, Rikhtegar et al., 2018) |          |                   |                                 |                                 |             |              |                    |                     | Significantly decreased Th17-associated parameters, such as Th17 frequency, expression levels of RORγt and IL-17 and also secretion level of IL-17 | No impact on IL-23 mRNA expression levels and IL-23 concentration |
| (Dolati et al., 2019) |          |                   |                                 |                                 |             |              |                    |                     | Significantly reduced the proportion of peripheral Treg cell frequency, and the levels of TGF-β, IL-10, and FoxP3 | |
| (Soveyd et al., 2017) | Iran    | Curcumin (capsule) | –                               |                                 | 80          | 66 (20)     | 20–50              | 60                  | Migraine                     | No significant change in ICAM-1 gene expression across groups ↓ ICAM-1 serum concentration in the combination group, and ω-3 alone at the end of the study compared to the beginning ↓ Attack frequency in the combination group |
| (Abdolahi et al., 2017) | Iran    | Curcumin (capsule) | –                               |                                 | 80          | 74 (20)     | 20–50              | 60                  | Migraine                     | Nanocurcumin alone did not show significant reduction either in mRNA or serum levels of TNF-α Combination of ω-3 fatty acids with nanocurcumin downregulated TNF-α and mRNA significantly |
| (Abdolahi et al., 2018) |         |                   |                                 |                                 |             |              |                    |                     | Nanocurcumin and ω-fatty acids downregulated IL-6, mRNA, and significantly decreased their serum concentration hs-CRP serum levels significantly decreased An additive reduction of IL-6 and hs-CRP in the combination group suggesting a possible synergetic effect |
| (Abdolahi et al., 2019) |         |                   |                                 |                                 |             |              |                    |                     | Nanocurcumin and ω-3 fatty acids downregulated COX-2/INOS mRNA Both drugs reduced serum levels and significantly reduced the frequency, severity, and duration of headaches | (Continues) |
| Author, year       | Country | Polyphenol (form) | Nanocarrier | Quantity administered (mg/day)/% | n (% males) | Trial duration (days) | Comparator/ control | Condition/parameter assessed | Outcome                                                                 |
|-------------------|---------|-------------------|-------------|----------------------------------|-------------|-----------------------|---------------------|---------------------------|--------------------------------------------------------------------------------|
| Parohan et al., 2019 | Iran    | Curcumin (capsule) | Nanomicelle (10) | 80 | 91 (27) | 18–45 | 56 | CoQ10, nanocurcumin, a combination of the two, or a placebo capsule | Migraine Significant effect of nanocurcumin and CoQ10 on frequency, severity, duration of migraine attacks, and HDR. Nanocurcumin and CoQ10 group had better scores in migraine-specific questionnaires at the end of the study compared to other groups |
| Masoodi et al., 2018 | Iran    | Curcumin (capsule) | Nanomicelle (−) | 240 | 56 (50) | 37 | 28 | Placebo capsule (both groups received mesalamine) | Ulcerative colitis Urgency of defecation Simple clinical colitis activity index |
| Bilia et al., 2018 | Italy   | Curcumin (capsule) | Nanocrystal (690–820) | 3000 | 29 (55) | 24–63 | 112 | Placebo capsule (both groups received acitretin) | Psoriasis Acitretin plus nanocurcumin significantly lowered psoriasis area severity index, while cholesterol serum levels remained unchanged |
| Amorndoljai et al., 2017 | Thailand | Ginger extract (gel) | Nanostructured lipid carrier (−) | 150 | 118 (14) | 50–75 | 84 | Diclofenac gel (1%) | Knee osteoarthritis Both nanodrug and 1% diclofenac gel significantly improved knee pain, stiffness, and physical function. Nanodrug produced a more significant reduction in pain by at least 50% |
| Hashemzadeh et al., 2020 | Iran    | Curcumin (capsule) | Nanomicelle (10) | 80 | 71 (15) | 55 | 42 | Placebo capsule | Knee osteoarthritis Scores of pain, stiffness, and physical activity subscales of patients of the nanocurcumin group compared with the placebo group |
| Javadi et al., 2019 | Iran    | Curcumin (capsule) | Nanomicelle (10) | 120 | 49 (10) | 20–80 | 84 | Placebo capsule | Rheumatoid arthritis The DAS-28, tender joint count, and swollen joint count at baseline and the end of the study were not significant between the treatment and control groups; however, the within-group values of each parameter reduced significantly compared to the baseline |
| Lueangarun et al., 2019 | Thailand | Mangosteen-polyphenol-rich extract (gel) | Polymeric nanoparticle (454) | 0.5% w/w twice-daily | 28 (14) | 25 | 84 | Clindamycin (1%) | Mild-to-moderate acne vulgaris Nanodrug showed significant reduction of comedones and inflammatory lesions. Nanodrug was significantly better at improving clinical severity |
| Pan-In et al., 2015 | Thailand | α-Mangostin (gel) | Polymeric nanoparticle (300–500) | 1.2% w/w (0.5 mg/cm²) | 10 (20) | 15–24 | 28 | Placebo gel base | Acne patients Significant improvement in acne vulgaris Insignificant skin irritation |
| Farhadi et al., 2018 | Iran    | Curcumin (capsule) | Nanomicelle (−) | 160 | 21 (48) | 24–77 | 10 | Placebo capsule | Thyroid carcinoma Frequency of micronuclei in the curcumin group was significantly lower after iodine-131 therapy |

(Continues)
| Author, year | Country | Polyphenol (form) | Nanocarrier (particle size, nm) | Quantity administered (mg/day)/% | n (% males) | Age | Trial duration (days) | Comparator/control | Condition/parameter assessed | Outcome |
|--------------|---------|------------------|---------------------------------|---------------------------------|-------------|-----|---------------------|-------------------|--------------------------|---------|
| (Delavarian et al., 2019) Iran | Curcumin (capsule) | Nanomicelle (10) | 80 | 29 (59) | 59 | 42 | Placebo capsule | Mucositis in head and neck cancers | No significant differences in WBC, RBC, platelets, and hemoglobin level before and after iodine-131 therapy |
| (Afshar et al., 2020) Iran | Curcumin (capsule) | Nanomicelle (–) | 120 | 54 (63) | 57 | 84 | Placebo capsule | Kidney disease | Statistically significant difference in the severity of mucositis. All control-group patients developed oral mucositis in the second week of radiotherapy; as opposed to only 32% of patients in the treatment group |
| (Alizadeh et al., 2018) Iran | Curcumin (capsule) | Nanomicelle (10) | 80 | 56 (100) | 30 | 70 | Placebo capsule | Infertility | Total sperm count, sperm concentration, and motility levels increased compared to baseline values for treatment group. Significant improvement in plasma levels of total antioxidant capacity, malondialdehyde, CRP, and TNF-α |
| (Sasaki et al., 2011) Japan | Curcumin in liquid form | Polymeric nanoparticle (190) | 30 | A: 7 (100) B: 14 (57) | A: 43 | 1 | Water free-form curcumin powder | A: Alcohol metabolism in healthy volunteers B: Bioavailability in healthy volunteers | Nanodrug had inhibitory action against alcohol intoxication and reduced acetaldehyde concentration of blood but had no significant effect on ethanol reduction. The AUC of nanocurcumin was 27-fold higher than that of free-form curcumin |
| (Motilva et al., 2016) Spain | Grapes—polyphenol-rich extract (wine) | Polymeric nanoparticle (–) | 1300 | 12 (50) | 19–50 | 1 crossover (14 day washout) | Red wine, red wine with free-form phenolic extract, and red wine with nanoencapsulated phenolic extract | Bioavailability and metabolism in healthy volunteers | The nanodrug slightly enhanced the urine excretion of malvidin-3-O-glucoside and its metabolites syringic and gallic acids |

-- Data not available.
*Values are min–max or mean.
AP-1, activator protein 1; AUC, area under the curve; BC, body composition; BP, blood pressure; CK-MB, creatine kinase myocardial band; CoQ10, coenzyme Q10; COX-2, cyclooxygenase-2; CRP, C-reactive protein; DAS-28, disease activity score of 28 joints; eAG, estimated average glucose; FBI, fasting blood insulin; FBS, fasting blood sugar; FoxP3, forkhead box protein P3; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HDR, headache diary results; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon gamma; IL, interleukin; INOS, inducible nitric oxide synthase; LDL-C, low-density lipoprotein-cholesterol; mRNA, messenger RNA; miR, microRNA; miRNAs, microRNAs; NAFLD, nonalcoholic fatty liver disease; NF-κB, nuclear factor kappa B; PCI, percutaneous coronary intervention; PDCD1, programmed cell death 1; QUICKI, quantitative insulin sensitivity check index; RBC, red blood cell; RORγt, retinoic acid-related orphan receptor gamma t; STAT1, signal transducer and activator of transcription 1; TC, total cholesterol; TG, triacylglyceride; TGF-β, transforming growth factor beta; Th17, T helper 17 cells; TNF-α, tumor necrosis factor alpha; Tregs, regulatory T cells; VCAM-1, vascular cell adhesion molecule 1; WBC, white blood cell; WC, waist circumference.
studies. The medical conditions assessed were grouped as cardiometabolic diseases, inflammatory diseases, cancer, or "other" and the impact of nanopolyphenols on these conditions is further discussed.

3.3.1 Cardiometabolic diseases

Cardiometabolic diseases covered in the 29 included studies can be divided into diabetes-related illnesses and cardiovascular diseases. The effect of nanouceretin gel was evaluated in patients with diabetic foot ulcer, while nanocurcumin capsules were administered to patients with diabetic neuropathy and diabetes to assess efficacy. It was found that nanoquercetin in combination with oleic acid significantly reduced wound healing time, while nanocurcumin produced antidepressant-like and antianxiety-like effects, reduced total score of neuropathy, and total reflex score and was also able to cause longitudinal changes in several glucose and lipid metabolism-related factors, such as HbA1c, FBS, and LDL in diabetic patients (Asadi et al., 2019; Asadi, Gholami, Siassi, Qorbani, & Sotoudeh, 2019; Gallelli et al., 2020; Rahimi et al., 2016). The epithelization caused by nanoquercetin is a result of its ability to upregulate angiogenesis markers, such as vascular endothelial growth factor and transforming growth factor beta 1 (Gopalakrishnan, Ram, Kumawat, Tandan, & Kumar, 2016).

The administration of nanocurcumin to overweight and obese patients with nonalcoholic fatty liver disease (NAFLD) resulted in improved inflammation, lipid, and glucose profiles compared to those who received placebos (Jazayeri-Tehrani et al., 2019). This amelioration of NAFLD by nanocurcumin was also attributed to improvements in fatty liver degree, waist circumference, and nesfatin, which is involved in the regulation of hunger. Nanocurcumin, however, had no significant effect on atrial and ventricular arrhythmias and other echocardiographic parameters in patients with unstable angina (Dashtani et al., 2019). Likewise, neither nanocurcumin nor a placebo treatment resulted in any significant differences in creatine kinase-MB and troponin I levels in patients with myocardial injury following elective percutaneous coronary intervention (Aslanabadi, Entezari-Maleki, Rezaee, Jafarzadeh, & Vahedpour, 2019). A positive role of curcumin in cardiovascular diseases was, therefore, not corroborated by these studies.

3.3.2 Inflammatory diseases

An array of disorders and conditions that are characterized by inflammation are included in this subgroup and included among them are multiple sclerosis (MS), migrane, colitis, psoriasis, arthritis, and acne vulgaris. Nanocurcumin was the drug of interest in all studies involving patients in this category with the exception of those with arthritis and acne who also used polymeric nanoparticles containing ginger and mangosteen extracts. Unlike the placebo capsules, nanocurcumin had the potential to inhibit neuroinflammation and was also able to restore the dysregulation of Th17 cells, restore the frequency and function of Treg cells, and to restore the expression pattern of dysregulated miRNAs (miRNAs) in the peripheral blood of patients with relapsing-remitting multiple sclerosis (Dolati, Aghebati-Maleki et al., 2018; Dolati, Ahmadi, Aghebti-Maleki et al., 2018; Dolati, Ahmadi, Rikhtegar et al., 2018; Dolati et al., 2019). An overproduction of interleukins (ILs), such as IL-17 by Th17 cells, can result in neuroinflammation and lead to the development of MS lesions (Qureshi, Al-Suhaimi, & Shehzad, 2019). Likewise, dysregulation of miRNAs involved in immune responses leads to autoimmunity as reported in several studies (Tufekci, Oner, Genc, & Genc, 2011). The effect of nanocurcumin as a neuroprotective and neuropharmacological drug in MS is, therefore, conveyed through several mechanisms thereby highlighting its therapeutic potential.

The effect of the administration of nanocurcumin to patients with migraine was compared to the effects resulting from ω-3 fatty acids or coenzyme Q10 (CoQ10), a combination of nanocurcumin with either of the two, or a placebo capsule. In most instances, the combination of nanocurcumin with ω-3 fatty acids was indicative of synergistic effects. This was evident in the combination resulting in a significant decrease in intercellular adhesion molecule 1 (ICAM-1) serum concentration and attack frequency, and the significant downregulation of tumor necrosis factor α (TNF-α), IL-6, and mRNA (Abdolahi et al., 2017; Abdolahi et al., 2018; Abdolahi et al., 2019; Soveyd et al., 2017). Similarly, the combination of nanocurcumin and CoQ10 synergistically reduced the frequency, severity, and duration of migraine attacks (Parohan et al., 2019). ICAM-1 is a proinflammatory factor that can lead to the release of inflammatory mediators and TNF-α is a major mediator of inflammation in most diseases/conditions (Hewlings & Kalman, 2017). The ability of nanocurcumin in combination with other therapeutics to impact
these factors suggests that they might play a vital role in the alleviation of various diseases or conditions, such as migraine that progress via inflammatory processes.

Nanocurcumin was also able to positively impact conditions, such as ulcerative colitis and psoriasis, in patients when compared to their respective placebo groups (Bilia, Bergonzi, Isacchi, Antiga, & Caproni, 2018; Masoodi et al., 2018). These effects of curcumin are again attributed to its anti-inflammatory effects and these findings have been corroborated in studies that assessed the activity of free-form curcumin in both in vitro and clinical trials (Hanai et al., 2006; Kang et al., 2016).

Along with nanocurcumin, polymeric nanoparticles prepared from crude ginger extracts were used to assess knee osteoarthritis and rheumatoid arthritis. The nanodrug made from ginger produced a more significant reduction in pain than that reported by the control group to whom a 1% diclofenac gel was administered (Amorndoljai, Taneepanichskul, Niemppo, & Nimmannit, 2017). Nanocurcumin also reduced pain scores, stiffness, and physical activity subscales of patients with knee osteoarthritis compared to the control group that received placebo capsules (Hashemzadeh, Davoudian, Jaafari, & Miftezi, 2020). Nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, are standard pain treatments but can result in a range of side effects (Hewlings & Kalman, 2017). The use of natural products can, therefore, be deemed preferential especially given their superior effects when nano-sized. This, therefore, means that both ginger extract and curcumin may offer an alternative to NSAIDS for patients with knee osteoarthritis who are experiencing negative side effects from standard treatments (Hewlings & Kalman, 2017). The use of nanocurcumin by patients with rheumatoid arthritis was, however, not as promising as no significant differences were observed between the nanocurcumin and control groups (Javadi, Haghighian, Goodarzy, Abbasi, & Nassiri-Asl, 2019).

The use of crude mangosteen extract and its main active principle, α-mangostin, in the treatment of acne was assessed. The controls used were clindamycin (1%) and a placebo gel base, respectively. The nanodrugs showed significant reduction of comedones and inflammatory lesions and significant improvement in acne vulgaris with no severe side effects or skin irritation (Lueangarun, Sriviriyakul, Tempark, Managit, & Sithisarn, 2019; Pan-In, Wongsomboon, Kokpol, Chaichana-wongsaroj, & Wanichwecharunguang, 2015). This also supports the favorable use of these nanodrugs over common acne treatments, which can result in several side effects (Tripathi, Gustafson, Huang, & Feldman, 2013).

### 3.3.3 Cancer

Nanocurcumin was administered to patients with different types of cancers, including thyroid carcinoma and head and neck cancer. The effect of nanocurcumin on chromosomal damages in peripheral blood lymphocyte by micronuclei assay in patients with differentiated thyroid carcinoma after therapeutic dose of I-131 was assessed (Farhadi, Bakhshandeh, Shafiei, Mahmoudzadeh, & Hosseinimehr, 2018). It was found that the frequency of micronuclei in the nanocurcumin group was significantly lower after iodine-131 therapy compared to the control group. Micronuclei assay is used to evaluate chromosomal damage in humans exposed to genotoxic agents (Joseph, Patwardhan, & Samuel, 2004). The lowering of the micronuclei frequency by nanocurcumin suggests a protective effect and indicates that it can prevent the genetic damage induced by I-131 in human lymphocyte.

The effect of nanocurcumin on oral mucositis in patients with head and neck cancer who are receiving radiotherapy was assessed (Delavarian et al., 2019). The severity of oral mucositis was found to significantly decrease in the treatment group compared to the control group. This finding has also been confirmed in other studies that examined the efficacy of free curcumin for this purpose (Normando et al., 2019). Nanocurcumin, therefore, has the potential to be a reasonable agent to hinder the development of oral mucositis in patients with head and neck cancer who require radiotherapy.

### 3.3.4 Others

The impact of the administration of nanocurcumin in patients with kidney disease and infertility was examined. The ability of the nanodrug to impact alcohol metabolism was also the focus of one study. The anti-inflammatory effects of curcumin resulted in the nanodrug lowering inflammation, high sensitivity C-reactive protein (hs-CRP) levels, and adhesion molecules ICAM-1 and vascular cell adhesion molecule 1 in hemodialysis patients (Afshar et al., 2020). There was, however, no significant impact on lipid-related markers, such as triglycerides, total cholesterol, and low-density lipoprotein cholesterol. The use of nanocurcumin in this regard might be beneficial; however, further studies would be needed.

Nanocurcumin capsules proved to be beneficial in the treatment of infertility as they were able to increase total sperm count, sperm concentration, and motility levels. There was also significant improvement in plasma levels of total antioxidant capacity, malondialdehyde, CRP, and TNF-α (Alizadeh et al., 2018). Similar results were reported for the impact of curcumin on bovine spermatozoa where an enhancement of spermatozoa activity was observed (Tvrdá, Lukáč, Jambor, Lukáčová, & Massányi, 2015). These findings suggest that treatment of asthenozoospermia with curcumin nanomicelle supplement could improve the quality of semen parameters.

The only parameter that was tested in healthy participants was alcohol metabolism and this was also the only study where nanocurcumin was administered in the form of a liquid supplement. Nanocurcumin had inhibitory action against alcohol intoxication and reduced the acetaldehyde concentration of blood (Sasaki et al., 2011). While there was a reduction in the concentration of the ethanol metabolite, no significant effect was found on ethanol blood concentration. This, therefore, means that nanocurcumin can possibly be used to moderate the effect of alcohol consumption by reducing the discomfort caused by acetaldehyde which results from the breakdown of ethanol. Since this study duration was only 1 day and the population size was only seven, further studies are needed to substantiate the findings.
3.3.5 | Pharmacokinetic properties

The pharmacokinetic properties of a drug determine its efficacy and safety. A drug must, therefore, reach its site of action in order to convey its desired effects, and as such, its bioavailability is critical. The low bioavailability of polyphenols is well known and must therefore be overcome in order for these molecules to produce successful therapeutic treatments. Two of the included studies assessed the bioavailability of nanoencapsulated polyphenols (Motilva et al., 2016; Sasaki et al., 2011). Nanocurcumin was used in one instance, while the nanoencapsulated grape phenolic extract was used in the other. It was found that the bioavailability of nanocurcumin was significantly enhanced compared to its free-form. While the nanoencapsulated phenolic extract did not significantly enhance the bioavailability of phenols, it slightly enhanced the urine excretion of malvidin-3-O-glucoside and its metabolites. This suggests that while the nanoencapsulation techniques and the experimental design appear to be suitable for the enhanced bioavailability of curcumin, they seem unsatisfactory for a similar outcome using a grape phenolic extract.

3.4 | Adverse events and limitations of the included studies

Adverse events reported after the use of nanopolyphenols in the included studies were minimal. Of the 18 studies that provided this information, a total of 12 studies reported no adverse effects during or after treatment (Abdolahi et al., 2018; Afshar et al., 2020; Alizadeh et al., 2018; Amorndoljai et al., 2017; Delavarian et al., 2019; Dolati, Aghebati-Maleki et al., 2018; Farhadi et al., 2018; Gallelli et al., 2020; Hashemzadeh et al., 2020; Javadi et al., 2019; Parohan et al., 2019; Sasaki et al., 2011). Mild adverse events reported include stomachache (Asadi et al., 2019; Asadi, Gholami, Siassi, Qorbani et al., 2019) and nausea (Jazayeri-Tehrani et al., 2019). The remaining studies reported multiple events with one study reporting flatulence, dyspepsia, headache, increased appetite, nausea, and yellow stool (Masoodi et al., 2018), while another reported minimal irritation, dryness, and itching (Lueangarun et al., 2019). There were also accounts of nausea, vomiting, mild cheilitis, and peeling of the palms and soles (Bilia et al., 2018). The latter effects were, however, identified as well-known and reversible effects of acitretin, which was administered to both the treatment and control groups.

One of the main limitations of the included studies is the small sample sizes used. In cases where the clinical trial was a pilot study, a small size is acceptable; however, larger cohorts are needed to validate results. Other limitations of the studies included short study durations and the administration of a single dose. Studies that did not use an identical placebo could also allow for treatment bias. Assessment of the most suitable dose and route of administration of the nanopolyphenol can also prove beneficial.

3.5 | Future prospects

Nanopolyphenols are intended to provide a targeted delivery of encapsulated phytochemicals, improve their sustained release from the nanoformulation, and thus enhance their bioavailability and therapeutic efficacy. These outcomes are possible based on their size, biocompatibility, surface chemistry, and relatively good stability. This application of nanoscale materials in medicine can, however, present different types of challenges, including biological, large-scale manufacturing, biocompatibility, safety, intellectual property, and government regulation challenges, along with challenges with the finished product being cost-effective in comparison to current therapies (Hua, De Matos, Metsetaar, & Storm, 2018).

The use of nanotechnology to aid the delivery of polyphenols and nutraceuticals in general will continue to increase globally. The rate at which innovative technologies are being developed confirms this. These technologies will, however, have to address the challenges previously mentioned for their safety, efficiency, and efficacy to be assured. Polyphenols are generally considered to be safe; however, there are several reports of adverse effect, which may result from their consumption. These effects have been evaluated predominantly in experimental studies and include factors, such as their possible interference with thyroid hormone biosynthesis, and the estrogenic activity of isoflavones (which can be beneficial or detrimental) (Mennen, Walker, Bennetau-Pelissero, & Scalbert, 2005). It has also been reported that the consumption of polyphenols can inhibit nonheme-iron absorption, which can lead to iron depletion in populations with marginal iron stores; and additionally, they can also interact with certain pharmaceutical agents and enhance or decrease their biologic effects (Mennen et al., 2005; Nagasako-Akazome, 2014; Samman et al., 2001). While the adverse effects resulting from the administration of nanopolyphenols in this review were all mild, the nanotoxicity of nanopolyphenols at specified doses has to be continuously monitored to ensure their safety.

Along with careful assessment of the polyphenol used in the construction of the nanodrug, the polymers used in the design should also be carefully selected and monitored (Rambaran, 2020). Advancement of our understanding of suitable polyphenol doses and apt design of the drug delivery systems to facilitate increased drug release, systemic circulation, and absorption while maintaining safety and efficacy is a fundamental step to developing the next generation of nanomedicines.

4 | CONCLUSION

The low bioavailability of polyphenols and their crude extracts causes their bioactivity to poorly translate to medical outcomes. This has served as an impetus toward the utilization of nanotechnology to enhance their efficacy.
The systematic review revealed that 29 clinical trials were conducted using nanopolyphenols. The main nanopolyphenol assessed in these trials was nanocurcumin, and capsules was the main form in which the nanodrug was administered to participants. Nanomicelles were the main nanocarrier used and the drug dosage ranged from 80 to 3000 mg/day. It is recommended that careful study is conducted to determine the nanotoxicity of this dosage. The medical conditions assessed were grouped and while negative findings were reported for the two studies that assessed heart disease, in almost all other instances, a more significant effect was reported for the treatment group that received the nanodrug. Studies that assessed pharmacokinetic effects also reported an increase in bioavailability. A move toward the use of clinical trials of suitable population size, study duration, and drug dosage to validate innovative nanopolyphenol formulations with medical claims is encouraged.

**CONFLICT OF INTEREST**

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

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