Prospects of ultrasonically extracted food bioactives in the field of non-invasive biomedical applications – A review

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ABSTRACT

Foods incorporated with bioactive compounds, called nutraceuticals, can fight or prevent or alleviate diseases. The contribution of nutraceuticals or phytochemicals to non-invasive biomedical applications is increasing. Although there are many traditional methods for extracting bioactive compounds or secondary metabolites, these processes come with many disadvantages like lower yield, longer process time, high energy consumption, more usage of solvent, yielding low active principles with low efficacy against diseases, poor quality, poor mass transfer, higher extraction temperature, etc. However, nullifying all these disadvantages of a non-thermal technology, ultrasound has played a significant role in delivering them with higher yield and improved bioefficacy. The physical and chemical effects of acoustic cavitation are the crux of the output. This review paper primarily discusses the ultrasound-assisted extraction (USAE) of bioactives in providing non-invasive prevention and cure to diseases and bodily dysfunctions in human and animal models. The outputs of non-invasive bioactive components in terms of yield and the clinical efficacy in either in vitro or in vivo conditions are discussed in detail. The non-invasive biomedical applications of USAE bioactives providing anticancer, antioxidant, cardiovascular health, anti-diabetic, and antimicrobial benefits are analyzed in-depth and appraised. This review additionally highlights the improved performance of USAE compounds against conventionally extracted compounds. In addition, an exhaustive analysis is performed on the role and application of the food bioactives in vivo and in vitro systems, mainly for promoting these efficient USAE bioactives in non-invasive biomedical applications. Also, the review explores the recovery of bioactives from the less explored food sources like cactus pear fruit, ash gourd, sweet granadilla, basil, kokum, baobab, and the food processing industrial wastes like peel, pomace, propolis, wine residues, bran, etc., which is rare in literature.

1. Introduction

As the population increases, several new human diseases also increase with new virus variants, bacteria, etc. Recently, coronavirus has proved this and controlling and preventing such diseases until the vaccines are invented remained the most challenging phase. Thus, humans rely on foods that have medicinal values, such as turmeric, garlic, ginger, cardamom, cinnamon, etc. Due to changes in environmental and health conditions, these nutraceuticals, functional foods, and food supplements have become the leading food factor to rely on and thus are the booming areas in food research in recent times. The term nutraceutical was coined by Dr. Stephen DeFelice, chairman of the Foundation for Innovation in Medicine, in 1989. Nutraceuticals can be a synonym for functional foods, preventing or treating diseases and disorders. Such functional foods with health claims have higher market value throughout the globe. Probiotic yogurt for improving gut health and immune is one best example [1].

As we all know, dates are rich in bioactive compounds such as phenolics and flavonoids, and the daily intake of dates should be 100 g to get 250–450 mg of total phenolic compounds (TPC). Instead of consuming dates in large quantities, the bioactive rich in TPC can be consumed to alleviate diseases such as hepatic steatosis, liver diseases, inflammation, & oxidative stress [2], which can be extracted with the help of alcohol and water [3]. Similarly, a hydroalcoholic extract of...
Moringa Oleifera seeds introduced via oral administration to rats at a dosage of 50–200 mg/kg led to a reduction of colon weight, indicating an anti-inflammatory effect on bowel illnesses [4]. According to the Food Drug Administration (FDA), the daily intake of 3 g of beta-glucan positively affects cholesterol reduction. Consumption of decaffeinated green coffee bean and beta-glucan as nutraceuticals positively affects glucose metabolism by reducing HbA1c levels [5]. Such bioactive-rich processed foods claiming heart health benefits, antimicrobial, anti-aging, anti-inflammatory, anti-cholesterol, and antihypertensive benefits upon consumption, are licensed for manufacturing with scientifically proven clinical data and are thus called nutraceuticals or functional foods under different regulations in different countries. Hence these bioactives may thus be used in non-invasive medical applications where the prevention of diseases is much more feasible apart from curing the conditions.

The bioactive compounds have higher significance in fighting against various diseases and dysfunction and gained considerable attention as a source of low-cost phytochemicals. The conventional method of extraction of bioactive compounds involves the process of maceration of sample in the solvent, with stirring or without stirring, at a particular temperature. This includes hot water extraction, solvent extraction, etc. However, conventional solvent extraction by maceration has significant drawbacks. These include insufficient recovery from the extracts, leading to the destruction of compounds like polyphenols which are sensitive to heat, involvement of toxic solvent, long-time extraction, and even a high level of energy consumption. Also, due to the toxicity of the solvent and the increasing price of fossil fuels, the replacement of such solvents has become crucial [6]. To overcome these issues, green technology comes into the picture for the extraction of natural compounds which possess higher benefits. Some of the green technology (non-conventional) includes ultrasound-assisted extraction (USAE), microwave-assisted extraction (MAE), pulsed electric fields (PEF), and subcritical and supercritical fluids extraction. Such technologies are faster and more energy-efficient and have higher mass and heat transfer in smaller equipment with minimal steps. The yield of extracting the bioactive compounds is many times higher than conventional extraction methods. The non-conventional method, ultrasound-assisted extraction (USAE), causes cell or food matrix disruption; releasing a significant amount of bioactive in a shorter time is the main feature and advantage of the technique [7].

USAE, a non-conventional extraction system, has been used recently in industries to extract different bioactive compounds from various food materials. The ultrasonic waves are induced by a transducer (probe or bath) [8], which triggers and forms the cavitation bubbles near the surface of the sample material. These acoustic cavitation bubbles have a more extensive surface area during the expansion cycle. When the size of these bubbles reaches a certain threshold, they collapse and emit massive amounts of energy. The released pressure and warmth created as microjets aim at the sample material’s surface and damage the cell walls by distributing the selective bioactive into the media. USAE process employs sound waves with a frequency more than human hearing, i.e., 20 kHz to 100 kHz, and the phenomenon of acoustic cavitation extracts compounds at less extraction time and lower amounts of solvent consumption. Compared to the conventional solvent extraction (CSE) approach, this phenomenon can boost solvent penetration and offer a greater region for mass transfer, resulting in improved extraction efficiency [9]. USAE bioactive compounds have various biomedical benefits such as antimicrobial properties, anticancer properties, antioxidant properties, and enhanced cardiovascular health from compounds such as phenolic compounds from wheat bran, coconut shell powder, citrus, and grapes; isoflavones from soya beans; volatile compounds from natural products; anthocyanins from grape seeds; flavanone glycosides from orange peel, etc. Significantly, the USAE process can be scaled up easily for industrial purposes [8]. The typical steps involved in the process USAE are represented in Fig. 1.

In the literature, though there are very many compilations of research majorly focussing on USAE of bioactive components [10,11], a combination of methodologies employed along with ultrasound to improve extraction [12,13] factors affecting extraction like temperature, solvent medium, etc., [14,15] and optimization of process variables during ultrasonication to improve yield and mass transfer are less [16,17]. Only a few discussions and sources of in-depth compilations are available on USAE bioactives and their bio-analytical assessments with application to non-invasive biomedical benefits [18,19]. Also, the little available information is only limited to a single bioactive component and its bioactivities [20,21]. Thus, this study aims to bring out the significant non-invasive biomedical benefits of USAE compounds from various food sources by reviewing and critically analyzing the bio-analytical assessments involving the in vitro, in vivo, and clinical research outcomes of recent research. Hence, our study would provide...

Fig. 1. A pictorial representation of the processing steps commonly adapted for ultrasound-assisted extraction (USAE) of bioactives.
food processors with potential non-invasive benefits, including antimicrobial, anticancer, antidiabetic, antioxidant, anti-cholesterol, heart health benefits, etc., from consuming the USAE bioactive or the foods enriched with USAE bioactives. Also, the review will explore the recovery of bioactives from the less explored food sources like cactus pear fruit, ash gourd, sweet granadilla, basil, kokum, baobab, and the food processing industrial wastes like peel, pomace, propolis, wine residues, bran, etc., which is rare in literature.

2. Antimicrobial benefits of USAE bioactives from various food sources and food wastes

E. coli and Staphylococcus aureus are pathogenic bacteria that can cause severe harm to humans [22]. If contaminated food, either in raw or processed form, is consumed, it can cause illness in humans [23]. Thus, the antimicrobial bioactive compounds extracted by ultrasonic processing are seen as a non-invasive biomedical application that can cure the illness caused by ingestion of spoiled foods [24], and by using them, we can prevent the infection or disease from occurring. The efficacies of major antimicrobial compounds are discussed in detail and are as follows.

2.1. Propolis

In a study, the propolis, a sticky brownish green product from the discharge of bees and bee wax containing many bioactive components like polyphenols and flavonoids, has antioxidant properties, antifungal, antiviral and anti-inflammatory properties, is extracted using ultrasound [25,26]. Many pharmaceutical and cosmetic products contain propolis in their compositions. The bioactive compounds of propolis are used for the application of food production because it is a natural preservative. Which is considered better and safe compared to the synthetic ones; the addition of propolis in food ensures the microbial stability and quality of the food during storage. The extraction yield increases due to cavitation bubbles that rupture and enhance shear, resulting in complete extraction. The components are combined more quickly by ultrasonic, making it simpler for the extracted material to come into contact with fresh solvents and continually eliminate the stationary layer barrier.

Furthermore, ultrasonic helps to break up the extracted material, increasing its exposure to the solvent. Furthermore, it enlarges the cell pores, allowing the solvent to enter the cells faster. All of the procedures above influence sonochemical effects between the substance and the solvent, resulting in increased extraction yields [27].

In a study, the antimicrobial activity of propolis extract was tested against bacteria, viruses, and fungi. The phenolic extract was prepared by shaking ultrasound-assisted extraction (SUAE), combining shaking extraction (SE) and USAE. The results showed that extract from SUAE had better antibacterial characteristics than SE and USAE. The SUAE showed inhibitory antimicrobial activity against various microorganisms such as bacterial like Staphylococcus aureus and Escherichia coli 0157 and fungi like Candida krusei, Mucor mucido, Alternaria solani, Colletotrichum gloeosporioides. Most of the strains showed growth inhibition zone of sizes ranging between 9.95 and 26.89 mm. The longer the ultrasonication time, the higher the antimicrobial activity of the propolis extracts. The most significant growth inhibition zones were obtained in all tested strains for the extract subjected to 20 min of sonication (SUAE). Among all the strains, S. aureus showed the maximum inhibition zone in all three extraction methods; however, the sample treated with SUAE for 30 min showed 27.07 mm of inhibition. It can be concluded that higher time for sonication and shaking has resulted in more significant microbial inhibition due to increased mass transfer [28]. In another study, the antibacterial and antiviral activity was assessed in both ethanolic and aqueous propolis extracts. The bioactivity was attributed to two flavonoids in propolis viz., quercetin and rutin. While the aqueous propolis extract had a higher rutin content, the quercetin content was about half that of the ethanolic extract. Propolis extracts at 0.1 g/ml have antibacterial activity, especially against P. aeruginosa and L. monocytogenes strains, which supports their usage in alternative medicines, and the efficacy was higher than the antibiotic ciprofloxacin at 5 µg [29]. The tricyclic compounds that contain free hydroxyl radicals in two flavonoid compounds result in more significant microbial damage: the greater the hydroxyl groups, the greater the damage. The processes by which these propolis chemicals impede bacterial activity and development include inhibiting bacterial cell division and creating cytoplasmic dysfunctions [29].

In a different in vivo study, a hydrogel made of propolis was effective against wound infection with S. aureus, and it showed enhanced wound healing properties at 300 µg/ml in the topical application. Based on the findings, it is shown that combining natural products like propolis and bee venom in chitosan gel could make a non-invasive medicine against wound infections in the future. Usually plants secondary metabolites have hydroxy groups present in the form of aromatic rings after the extraction process which will help in donating free electrons which in turn results in antioxidant activity. The healing properties of propolis were due to flavonoids’ anti-inflammatory, collagen synthesis, and antibacterial activity. The caffeic acid phenethyl ester in propolis has an immunosuppressive effect on T-cells, making them responsible for inflammatory disorders. Furthermore, it inhibits the expression of interleukin-2 (IL-2) genes and the production of IL-2 in activated T-cells [30]. Thus, the new antibiotics in the form of antimicrobial compounds are urgently needed to limit the spread of harmful microorganisms that have developed resistance to present antibiotics and give medicines for chronic and severe diseases such as wounds and malignancies. Even though much research has been done on the biosynthesis of desirable chemical molecules that bestow possible biological effects and therapeutic efficacy, there are still more potent and physiologically active compounds for investigation, particularly from food resources.

2.2. Batal leaves

In a new study, for the extraction of Cyclocarya paliurus flavonoids (CPF) or Batal-based flavonoids in liquid form, an enzymolysis-ultrasonic aided extraction (EUAE) method was devised, and refined CPF was obtained. The disc diffusion method was used to test antimicrobial activity. At a concentration of 80 g/mL, the inhibition zone diameters of Cyclocarya paliurus flavonoids against Staphylococcus aureus, Salmonella, and Escherichia coli were 21.5 ± 0.45, 17.5 ± 0.35, and 13.5 ± 0.25 mm, respectively. These findings suggested that the flavonoids found in Cyclocarya paliurus could be used as antibacterial and antioxidant agents in pharmaceuticals, functional foods, and natural cosmetics. The number and position of hydroxyl groups present in flavonoid greatly influence the activity. The extraction yield of Cyclocarya paliurus flavonoids was 34.24 mg/g at optimal extraction conditions. This increase in the yield was due to increasing ultrasonic time that enhanced the power of cavitation the time required to show effective extraction was 10–30 min because increasing the period more than that can affect the heat-sensitive flavonoids [31]. When CPF stresses gut microorganisms, they may up-regulate proteins associated with defense mechanisms to protect cells, while down-regulated proteins are involved in metabolism and biosynthesis [32].

2.3. Cactus pear

The cactus pear is a fruit (Opuntia ficus indica) abundant in dry regions of the globe. The seed contains 98.8 g/kg of oil, which is high in omega-3 fatty acids. It’s a good source of polyphenols as well. It was analyzed by Ortega-Ortega et al. that the highest yield was obtained at the highest amplitude level of 92 percent, and the ultrasonic extraction yield ranges from 3.75 to 6 percent. High amplitudes are essential for oil production because they boost the cavitation effect, which causes physical alterations to the seed’s structure, such as disruption of cell walls, reduction in particle size, and expansion of the exposed area.
These physical changes help in the formation of several hydroxyl groups that increases the antimicrobial ability of the extract. These circumstances can make it easier for the solvent to extract the oil and penetrate the soil. After 10 min of treatment, the maximum yield was attained; prolonged treatment times (15 min) at high amplitudes (90 percent) did not improve oil extraction. This could be explained by the cell walls initially completely breaking down in the first few minutes of the cavitation impact, for its high antioxidant activity due to the presence of polyphenols and polyunsaturated fatty acids, which in turn act as an antimicrobial agent against certain microorganisms like E. coli. Cactus pear powder was examined under a scanned electron microscope before and after the ultrasoundication. It shows that son physical changes such as intact cells were damaged, and starch granules were damaged because the cavitation phenomenon disrupted the cell structures of the seeds [33]. The optimum ultrasound extraction conditions were of 78 % amplitude for 10 min and yielded antioxidant activity values of 66.25 mg (Antibody Affinity extraction) AAE/100 g and 289 μmol (Trolox Equivalent) TE/100 g for (2,2azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) ABTS and (1,1-diphenyl-2-pierylhydrazyl Assay) DPPH activity, respectively. The results showed higher effectiveness of ultrasound than the conventional method for reducing the E. coli concentration of 10⁸ cfu/ml. The maximum inhibition zone for gram-negative E. coli was 15.56 mm with 7.78 μl of USAE Cactus pear oil and 18.89 mm for gram-positive Staphylococcus aureus at 9.17 μl. In a study, wound healing properties of Opuntia ficus indica seed oil are demonstrated on animal models by full-thickness skin excisional model. The seed oil rich in unsaturated fatty acids, triacylglycerols, phytosterols, and tocopherols provided anti-inflammatory, angiogenic potency, supply of nutrients for multiplication of fibroblast and for hastening up the arrangement of the dermal extracellular matrix. Also, unsaturated fatty acids helped repair the affected tissues and provided hydration and faster scarring. Additionally, the oil had substantial antibacterial activity against bacteria (Enterobacter cloaceae), yeasts (Candida parapsilosis and Candida sake), and fungus (Aspergillus niger, Penicillium digitatum, and Fusarium oxysporum) by disturbing the ATP production providing an overall wound healing effect [34]. Also, the prickly pear Opuntia ficus-indica (L.) seed oil showed antibiofilm activity with its capacity to block the metabolic changes taking place in the microbial cells included in the biofilm. The 8 μl/ml of oil inhibiting metabolism of 96.26 % of Escherichia coli, 64.97 % of Pseudomonas aeruginosa, 64.97 % of Listeria monocytogenes, and 98.35 % of Pectobacterium carotovorum in the biofilm. Thus, it can be used in processed food products to enhance shelf life, and this type of study can be extended to prevent pathogenic diseases in humans by accidentally ingesting spoiled foods [35]. In a different study by R.Bia et al. [36], the authors have found that the unsaponifiable fraction of O. ficus indica seed oil is far more effective than the glyceridic fraction against all dangerous microorganisms, particularly again Escherichia coli, especially by the bioactives like polyphenols, terpenic components, terpenic alcohols, and aliphatic alcohols and their radical scavenging activity. One mode of action might be membrane rupture, which inhibits bacteria adhesion, enzymes, and protein transport, inhibiting the involvement of target nucleic acid synthesis and energy metabolism [37,38].

2.4. Pomegranate peels

In a similar study, the pomegranate peel powder and USAE aqueous extracts of goji berries encapsulated with little maltodextrin content with high polyphenol content displayed antibacterial activity, suggesting that they could be used in food preservation or plant protection. The antifungal activity against the mold Aspergillus niger was most viable with a 6.2 min and 60 % ultrasound amplitude. The mean diameter of the inhibitory zone of Aspergillus niger was 17.7 mm and has shown to be effective at a concentration of 3000 μg/mL. At this sonication parameters, the total phenolic compounds (TPC), 1,1-29 diphenyl-2-pierylhydrazyl free radical scavenging (DPPH), ferric reducing-antioxidant power 30 (FRAP), and half-maximal of radical-scavenging activity (IC50) were 13.1 percent, 42.2 mg (Gallic acid Extract) GA/g, and 1824.6 mol Fe (II)/g and 0.51 mg/mL, respectively, and these were used against the inhibition of concerned microorganisms also the pictorial representation was mentioned in Fig. 3 [39]. The most commonly accepted mechanism of polyphenol antibacterial action is based on morphological changes in bacterial cells, such as cell disruption, releasing of the cytoplasmic membrane, the emergence of ghost-like germs, and cell deformation [40]. According to the results, increasing ultrasonic amplitude leads to a more considerable cavitation effect, which enhances the extraction process. Furthermore, cavitation-induced hydroxylation of phenolic compounds’ aromatic rings may result in an increase in antibacterial content. The increase in extraction yields, it was also noted, cannot be only attributable to the abrasive or turbulent effects of ultrasonic waves but also to the sonophysical effects on the particle surfaces. The cavitation phenomena in ultrasonic processing raise plant tissue permeability. Due to the breakdown of some active natural products, higher ultrasonic intensity might also harm extracted components; therefore, adjustment is required [39]. A 15-day clinical trial was performed against oral candidiasis in rats, with different quantities of this pomegranate peel extract (125, 250, and 500 g/mL/kg) and nystatin (100000 U/mL/kg). After treatment, a significant improvement in oral candidiasis, regardless of the concentration of pomegranate peel extract, could be used as a natural alternative non-invasive medicine [41]. Another study found that an alcoholic extract of the fruit peel of P. granatum could help manage coccidial parasites in broiler chickens. Based on oocyst production decrease, mean weight gain of birds, and feed conversion ratio, activity was assessed compared to the reference medication amprolium. The output of oocysts was assessed using the Mc-Masters counting method. The crude methanolic extract (CME) of the fruit peel of P. granatum had the most excellent anticoccidial activity, as evidenced by oocyst output reduction (92.8 ±15.3), weight gain of birds (1403.0 ±11.9 g), and feed conversion ratio (1.66 ±0.04), indicating the presence of alcohol soluble active ingredients in the plant [42]. In addition to its historical applications, pomegranate is employed in various medical systems, including Ayurvedic medicine, where it is used as an anti parasitic agent [43]. According to Dkhil, 2013 the fruit peel of P. granatum is antihelminthic and protects against E. papillata-induced coccidiosis. Pomegranate peel’s therapeutic benefits are attributed to polyphenols, mainly [44].

2.5. Orange peels

In another study on USAE, the antibacterial activity against Staphylococcus aureus, Bacillus cereus, and Salmonella typhimurium was noted for extracted polyphenols from the peels of the kinnow (Citrus reticulate L.). The researchers concluded that 80 % methanol extracted polyphenol compounds using UAE containing 32.48 mg gallic acid equivalent (GAE/gm of extract) were superior to 80 % ethyl acetate extract containing 8.64 mg (GAE/gm extract) using the maceration technique. The 500 μg/ disk concentration showed an inhibition zone of 8.67 mm against Staphylococcus aureus, but no inhibition was detected in the case of Salmonella typhimurium. Similarly, 750 μg/disk concentration showed a 14 mm inhibition zone for Staphylococcus aureus and a 7.33 mm inhibition zone for Salmonella typhimurium. The highest inhibition was seen for a higher concentration of diffused compound, i.e., 1000 μg/disk. For Staphylococcus aureus, it was 16 mm; for Salmonella typhimurium, it was 9.0 mm. It can be concluded that kinnow peel extract has shown maximum inhibition against Staphylococcus aureus and most negligible inhibition towards Salmonella typhimurium with the same concentration. Therefore, kinnow mandarin peels might be employed as a functional food additive as a possible source of phenolic compounds with antibacterial capabilities [45]. The change in the chemical structure due to addition of hydroxyl radicals to form phenol groups that helps in the antibacterial activity and is represented in the Fig. 2. For example, such an additive can be used on minimally processed foods and wherever the probability of hand contamination is higher on food-borne infections or...
intoxications. Dental caries is a severe oral health condition affecting humans for many years. While Streptococcus mutant bacteria is the primary cause of tooth decay, Lactobacilli bacteria are known to exacerbate pre-existing caries. An in vitro study on the hot ethanolic extract of Citrus sinensis peel showed the most significant reduction in dental caries, followed by the cold ethanolic extract for the bacteria. Hot and cold ethanolic extracts of Citrus sinensis peel had a minimum inhibitory concentration of 12–15 mg/ml against both dental caries bacteria. They also found that the aqueous extracts were effective at very high concentrations. The tannins, saponins, phenolic chemicals, essential oils, and flavonoids are responsible for the antibacterial properties of peels. These chemicals are recognized to be physiologically active, which aids the plant’s antibacterial capabilities [46]. Thus, the kinnow orange peel can also be studied for action against dental caries, and such non-invasive medical benefits can be obtained by incorporating such natural compounds in toothpaste. The findings of another study on kinnow show that extracts of the plant have solid antibacterial activity in vivo and in vitro against some clinically meaningful bacterial and fungal strains, such as Gram-positive bacteria (B. cereus, S. aureus, and S. epidermidis) and Gram-negative bacteria (E. coli, P. aeruginosa, P. vulgaris, and S. typhimurium) and fungi C. albicans and T. viride confirming the plant’s utility as traditional medicine. Phytochemical analysis of active extracts of kinnow peel showed the presence of polyphenols and alkaloids providing antimicrobial benefit [47]. The citrus fruit peels are exceptionally high in flavanones and polymethoxylated flavones, which are uncommon in other plants [48]. Thus, the waste from the citrus processing industry, mainly the peels, can be exploited as a natural drug, like a non-invasive medicine, as these are a potential source of rich secondary plant metabolites and essential oils. In a similar study, the EOs from bitter orange peel were extracted using an
ultrasonic-assisted hydro distillation process. The optimal EOs have high antibacterial activity against *E. coli*. These bitter orange peel essential oils could be used as dietary and medicinal supplements because of their antioxidant, antibacterial properties, and healthful compositions [49]. Their influence supports the antibacterial action of essential oils on cell membrane permeability, which causes disruptions in meaningful activities such as nutrition processing, structural macromolecule synthesis, energy production, membrane transport, and growth regulators [49]. The antibacterial action of essential oils is supported by their influence on cell membrane permeability, which causes disruptions in essential activities such as nutrition processing, structural macromolecule synthesis, energy production, membrane transport, and growth regulators [49].

2.6. *Tulsi/Basil*

Table 1 represents the antimicrobial activity of USAE bioactive from various plant materials. Even in wealthy countries, microbial infections have become a serious hazard to healthcare systems. Essential oils (EOs) are still a little-studied strategy for controlling infectious diseases. Moreover, USAE of essential oil production has emerged as a promising source of bioactive volatiles compared to traditional methods. Most antimicrobials are no longer effective against *Mycobacterium tuberculosis*, the tuberculosis causative agent. As a result, it is difficult to cure all tuberculosis patients, and the global incidence of tuberculosis caused by drug-resistant *M. tuberculosis* is expected to rise in the future. As a result, new anti-microbials against *M. tuberculosis* must be discovered and developed as soon as possible. Hydro distillation was used to extract essential oil from leaves of *Ocimum sanctum* L (*Tulsi/Basil*). Using varying quantities of EOs, the anti-mycobacterial action was investigated in the BD BACTEC MGIT instrument against H37Rv and nine clinical isolates of *M. tuberculosis*. H37Rv had a minimum inhibitory concentration of 3 ml (2.931 mg), while clinical isolates of *M. tuberculosis* had concentrations ranging from 1.5 ml (1.4655 mg) to 6 ml (5.862 mg). In the *in vitro* BD BACTEC MGIT technique, the essential oil from the leaves of *O. sanctum* L (*Tulsi/Basil*) possesses anti-*M. tuberculosis* activity [50]. Essential oils affect cellular architecture, resulting in membrane integrity breakdown and increased permeability, which disrupts various cellular activities, including membrane-coupled energy production, cell membrane transport, and other regulatory functions. The disruption of cell membranes by essential oils may help in a variety of critical tasks such as energy transformation, sustenance handling, underlying macromolecule combination, and development controller emission [51].

In this study, a combination extract (EOT) including extracts from *Ocimum basilicum* and *Trifolium pratense* was used for the first time to establish its therapeutic impact on cutaneous disorders. To assess the wound healing impact of EOT, a novel gel formulation was developed and tested in *vitro* (using the scratch test assay) and in *vivo* (on an animal model). *In vitro* investigations demonstrated that it recovered entirely when the dermal fibroblast monolayer was treated with EOT at a concentration of 50 µg/ml. In vivo investigations using a hydrogel formulation based on EOT revealed improved wound contraction time and complete healing after 13 days of therapy. In addition, a clinical case of *Psoriasis vulgaris*, in which one week of treatment resulted significantly improved the patient’s health. Applying a unique gel formulation containing EOT topically to the skin is a viable therapeutic alternative for treating skin problems. The active chemicals in the extract (polyphenols, flavonoids, and volatile oils) are engaged in immune system stimulation and provide anti-inflammatory, antibacterial, and antioxidant properties for wound healing. Hydroxyl groups released by USAE will add to a combination, and development controller emission [51].

Table 1

| S. No | Materials | Extracts | UAE Conditions | Target microorganism | Efficacy/Inhibition zone | References |
|-------|-----------|----------|----------------|----------------------|-------------------------|------------|
| 1.    | *C. paliurus* (Sweet Tea Tree) | Flavonoids | Temperature: 50°C, pH: 5.08, Complex Enzyme Condition: 3.23 % Power: 100 W, Time: 10-60 min Frequency: - | *Staphylococcus aureus* | 21.5 ± 0.45 mm | [193] |
|       |           |          |                | *Salmonella*         | 17.5 ± 0.35 mm          |            |
|       |           |          |                | *Escherichia coli*   | 13.5 ± 0.25 mm          |            |
| 2.    | *E. glauophyllum* (Waxyleaf Nightshade) | Phenols | Ethanol: 50 %, Solvent: Solid ratio (20:1 ml/g), Temperature: 40°C, Power: 400 W, Time: 10 min | *Salmonella enteric* | 0.432 ± 0.006 mm | [195] |
|       |           |          |                | *Listeria innocua*   | 0.252 ± 0.022 mm        |            |
|       |           |          |                | *Staphylococcus aureus* | 0.556 ± 0.002 mm        |            |
| 3.    | *L. sativum* (Garden Cress) | Phenols | Ethanol: 70 %, Solvent: Solid ratio (20:1 ml/g), Temperature: 50°C, Frequency: 45 kHz, Time: 20 min pH: - | *Staphylococcus aureus* | 12 mm (FDSS) | [155] |
|       |           |          |                | *Pseudomonas aeruginosa* | 16 mm (DSS)           |            |
|       |           |          |                | *Proteus mirabilis* | 9 mm (FDSS)            |            |
|       |           |          |                | *Staphylococcus epidermidis* | 12 mm (FDSS) |            |
|       |           |          |                |                     | 15 mm (DSS)            |            |
| 4.    | *Citrodea Palau leaves* (Lemon Beebrush) | Essential oil | Solvent: Solid ratio (600: 30 ml/g), Power: 100 W, Temperature: 25°C, Frequency: 30 kHz, Time: 45 min pH: - | *Escherichia coli* | 22.10 ± 0.16 mm | [194] |
|       |           |          |                | *Pseudomonas aeruginosa* | 18.84 ± 0.22 mm        |            |
|       |           |          |                | *Staphylococcus aureus* | 24.42 ± 0.23 mm        |            |
|       |           |          |                | *Salmonella*         | 27.57 ± 0.19 mm         |            |
|       |           |          |                | *Typhimurium*        | 23.22 ± 0.23 mm         |            |

FDSS = Freeze Dried Sprouts Sonification, DSS = Dried Sprout Sonification.
the aromatic rings of flavonoids or phenolic compounds. This efficiency increase is due to the sonochemical effect (synergistic effect) of the two solvents that causes changes in the molecules and increases the healing effect [52].

2.7. Hawthorn fruit

In a different study, antimicrobial activities of the colorants from the Hawthorn fruit powder obtained by the UAE process are used to dye textiles fabrics. The three main flavonoids, Quercetin, Iutin, and Kaempferol, were successfully used to dye polyamide (Nylon 6) fabric upon extraction in various solvents. The colorants showed antimicrobial activity against E. coli and S. aureus. The presence of high phenolic components in the extracted colors from hawthorn fruits was linked to the enhancement of increasing in the hydroxyl groups provided by USAE method, which in turn increases the interaction among the molecules and was proportional to the number of adsorbed colors on the fabric. At the 0 % dye (On the basis of Wet Fabric) there was 0 % reduction in E. coli and S. aureus while at 50 and 100 % of dye (o.w.f) the percentage reduction was 59.71, 90.85 (E. coli) and 46.64, 81.42 (S. aureus) and the inhibition zone values (mm) were 0.85, 4.40 (E. coli) and 0.67, 3.56 (S. aureus) it showed significant antimicrobial properties against about two micro-organisms. The sonochemical impact of the two solvents increased the range of flavonoid compounds and opened more channels in the cellular matrix of fruit, boosting efficiency. Sadeghi-Kakhkani et al. showed this effect for the first time [53]. Hawthorn fruit extract’s role in curing periodontitis in Wistar rats by Hatipoglu et al [54]. Periodontitis is an oral cavity disease caused by a combination of tooth bacteria plaque and the human response and is characterized by gingival inflammation, periodontal pocketing, and alveolar bone loss. This condition worsens due to the host’s production of inflammatory cytokines and reactive oxygen species by polymorphonuclear leukocytes. This work studies hawthorn extract and its effect on serum oxidative status and alveolar bone loss. By modulating TAS (total antioxidant status), TOS (total oxidant status), and OSI (oxidative stress index) levels in periodontal tissues, hawthorn extract inhibited periodontal inflammation and alveolar bone loss for 11 days [49]. The positive changes are due to hawthorn extract’s antimicrobial, antioxidant, and anti-inflammatory properties [55]. Hawthorn leaf extract with high quantities of polyphenol (140.67 ± 3.17 μg equivalent of gallic acid/mg of extract) was employed in a study for methicillin-resistant Staphylococcus aureus and S. epidermis. The significant presence of phytochemical families such as flavonoids and phenolic compounds has given the antibacterial properties of hawthorn leaf extracts. The minimum inhibitory concentration ranged from 4.00 to 16.00 mg/ml [56]. Diverse modes of action of the flavonoid group have been disclosed; for example,

| Table 2 | Different bioactive compounds from various food sources and their non-invasive anticancer activity. |
|--------|-------------------------------------------------------------------------------------------------------------------------------------|
| S. No | Food source | Name of bioactive compound | Anticancer/anti-tumour activity | Yield | Dosages | References |
| 1 | Olive leaves | Flavonoids | Strong cell viability on HeLa cell lines (cervical cancer) | 74.95 mg RE/g dm | 1.60 mg/ml | [92] |
| 2 | Elephant ears leave (Bergenia emeiensis) | Triterpenes | Induce HeLa cell apoptosis via a mitochondrial pathway | 137.08 ± 3.67 μg UAE/g | 25 μg/ml | [93] |
| 3 | Red seed weed (Porphyra haitanensis) | Polysaccharides | Arrest the proliferation of HT-29 cells | 20.53 % | 664.4 μg/ml | [94] |
| 4 | Garden asparagus (Asparagus officinalis) | Polysaccharides | Inhibit the human leukemia cells (HL-60, HeLa cell lines) | 3.1 % | 10 mg/ml, 200 μg/ml | [95] |
| 5 | Florist daisy (Chrysanthemum morifolium) | Flavonoids | Inhibit the proliferation of MKN45 cells | 5.24 % | 20 mg/ml | [96] |
| 6 | King trumpet mushroom (Pleurus eryngii) | Phenolics | Anti-proliferation activity against Caco-2 cells, HepG2. | 13 % | 800 μg/mL | [97] |
| 7 | Pot marigold (Calendula officinalis) | Phenolics | Inhibits the breast cancer cell line Hs578T | 32 % | 749.4 μg/mL | [98] |
| 8 | Chuan xiong (Ligusticum chaenom) | Polysaccharides | Slight inhibition of hepatocellular carcinoma cells (HCSS) | 4.08 % | 400 μg/mL | [99] |
| 9 | Mushroom (Holothuria solvate) | Polyphens | Inhibition of HeLa cell viability and early apoptosis noticed on HeLa cells | 0.62 ± 0.08 % | 50 μg/mL | [100] |
| 10 | Red kidney bean | Quercetin | Inhibition of B16-F10 cells also stops the P13K/AKT pathway | 1.33 % | 17.88 ± 1.28 μg/mL | [101] |
| 11 | Great St. Johnswort (Hypericum ascyron) | Quercetin and Kaempferol | Polyaccharides | The combination of quercetin and kaempferol inhibits the apoptosis of HeLa cell lines | 98 % | 25 μg/mL | [102] |
| 12 | Green dragon (Pinellia ternata tubers) | Polyaccharides | Restrict the apoptosis of Hep G2 cells via a mitochondrial pathway | 4.94 % | 400 μg/mL | [103] |
| 13 | Grape skin | Anthocyanins | Effective arrest/apoptosis of breast cancer cells & no effect on normal breast cells | 3.01 ± 0.04 % | 2.5 to 10.0 μg/mL | [63] |
| 14 | Chinese dates | Polyaccharides | Apoptosis of HeLa cells (cervical cancer) or cell shrinkage | 1.97 ± 0.08 % | 164.6–87.1 μg/mL | [67] |
| 15 | Kokum | Polymemols | Effective cell death of MCF-7 breast cancer cells | 54 ± 2.1 % | 60 μg/mL | [87], [71] |
| 16 | Mango Pomace | Polysaccharides | Inhibitory activity against proliferation of HepG2, MCF-7, A549, HeLa, A2780, HCT-116, and BGC-833 cells | 3.98 % | 1000 μg/mL | [71] |
| 17 | Blueberry | Anthocyanins | Cell cycle arrest in HepG2 cells and no toxicity in HE-7702 cells | 9.32 ± 0.08 mg/g | 0.1 to 10 μg/mL | [76] |
| 18 | Raspberry | Anthocyanins & pectinase | Polyphens | Cell death in A549 and MCF-7 cells | 0.888 mg/g | 20 μM | [80] |
| 19 | Purple basil leaves | Polysaccharides | Apoptosis of Caco-2 cells | 200 ml | 400 μl/ml | [84] |

Caco-2: human colon adenocarcinoma; A549: adenocarcinomas human alveolar basal epithelial cells; MCF-7: Michigan Cancer Foundation-7; HL-7701- Normal Human Liver Cells; HepG2- human hepatoma cell lines; HeLa- Henrietta’s cancer cells; A2780- ovarian cancer cell line; HCT-116- human colorectal carcinoma cell line; BGC-833- Celsallosa cell line; HepG2- human hepatoma cell lines; B16-F10- murine melanoma cell line; HCSS-hepatocellular carcinoma cells; Hs578T- epithelial cells isolated from breast tissue derived from a 74-year-old, White, female breast cancer patient; MKN45- Celsallosa cell line; HL-60- human promyelocytic leukemia cell line; HT-29- human colorectal adenocarcinoma cell line; P13K/AKT pathway- Protein Kinase B; μM- Micrometer; μg- microgram; UAE- ursolic acid equivalents per gram; RE/g dm- routine equivalent/g dry matter.
baicalein can reverse methicillin-resistant Staphylococcus aureus (MRSA) ciprofloxacin resistance via an auxere protein (Nora) efflux pump inhibitory effect, and inhibition of MRSA virulence factors such as pyruvate kinase might lead to an ATP [56].

3. Anticancer benefits of USAE bioactives from various food sources and food wastes

Cancer is the second most major health problem globally, after heart disease. Scientists have proposed many routes to treat cancer for many decades; still, there are many difficulties in inhibiting the spread of cancer within body parts. Here, the potential of ultrasound to engineer functional foods to extract bioactive compounds targeting cancer is provided. For food sources such as mango, jujube, grape skin, etc., [59], and their yields, dosages, and anticancer activity are mentioned in Table 2. According to the World Health Organization (WHO), new cancer and death cases will rapidly be increased in 2021. There are 2.26 million new cases and 1.80 million death cases for lung cancer; 1.93 million new cases and 1.79 million death cases for breast cancer [60]. There are 3 cancer cell lines or subtypes: estrogens receptors, human epithelial growth factor receptors, and triple-negative breast cancer (TNBC). Among these types, TNBC is very difficult to cure, and many studies are in progress to determine the treatment for this subtype. This condition gives a meager survival rate compared to the other two types [61].

3.1. Grape skin

Mostly grape skins are considered waste material in the juice industry, but they can be used as a by-product, which contains many bioactive compounds, one of which is anthocyanins which are very useful in treating cancer [62,63]. Grape skin powder was extracted for anthocyanins by using the ultrasound-assisted enzyme extraction method (USAEM) using pectinase at 0.16 %, and the maximum yield was 3.01 ± 0.04 mg/g at 50 °C, 28 min, and ultrasonic power of 400 W. Further, 200 ml of anthocyanin extract obtained from under optimized conditions (AEOEC) were purified. Those components are named components I & II, with the purity of 91.35 and 92.64 %, respectively. This study indicates that as the pectinase dosage increases, there is no effect on yield, merely as the extraction time increases the yield of anthocyanins. The cavitation effect, localized pressure, and temperature in the solvent into the grape skins, which promoted the release of hydroxyl radical and form intracellular anthocyanins into the solvent and thus improved the anthocyanins yield [63]. Before testing for anticancer activity, these AEOEC components I & II were loaded into cancer cell cultures MCF-7 (cancer breast cells) and MDA-kb2 (normal breast cells) with concentrations ranging from 2.5 to 10.0 µg/mL. AEOEC showed an effective result on cancer cells compared to component I and component II, which notifies that it is a suitable dosage for cancer cell inhibiting. The dosage ranging from 2.5, 5.0, 10.0 µg/mL of AEOEC extract showed apoptotic effect on MCF-7 cancer cells at percentage ranging from 25.36 ± 0.69 %, 31.22 ± 0.85 %, and 50.21 ± 1.31 %, respectively. Also, these dosages showed apoptosis on MCF-7 cells in the G0/G1 phases drastically reduced; nonetheless, the proportion of cells in the S phase was not substantially different among the three dosages of AEOEC-treated cells groupings. The AEOEC treatment ranged from 2.5 to 10.0 g/mL and raised the proportion of cells in G2/M stages concentration-dependent compared to cells in the vehicle control group. These findings indicated that MCF-7 cells were arrested in the G2/M phase, concluding that these grape’s by-products (skin) can be used for cancer treatment [63]. The component fastens the disease cell apoptosis by increasing the expression of apoptosis-related proteins while decreasing the expression of apoptosis inhibitory factors. Insensitivity to grape skin product (GSP) appeared to be conferred through increased B-cell lymphoma 2 (Bcl-2) levels and inhibition of caspase-3 activation [64]. In different studies, the extraction of anthocyanins from grapes using solvent extraction methods showed 31.2 ± 0.33 %, and a 100 µmol/L showed cell viability on HT-29 cells. When these cells are incubated with anthocyanin-rich extract for 2 days results in the activation of Caspase 3; this activation shows the apoptosis of cells [65]. Similarly, Muscadine grape skin extract (MGSE) with anthocyanins, the main bioactive compound, has the potential for bone turnover, migration, and antagonizing snail signaling pathway and breast cancer progression. In vitro and in vivo studies showed that treatment of this extract for 3 days decreased snail expression and Cat L activity in C4-2 cells for the first time. This shows that this grape extract has potential for snail-mediated osteoclast genesis in prostate and breast cancer cells. This is the first report showing MGSE inhibits bone turnover via Cat L [66].

3.2. Jujubes

Next, the polysaccharides of Jujube (Ziziphus jujuba) seeds are extracted by ultrasound-assisted heating extraction, and the USAE condition is 100 min, 83.1 °C, and 140 W. The extraction procedure of ZJSPs-1 is mentioned in Fig. 4. The anti-tumor activity of ZJSPs-1 was conducted using HeLa cell lines in vitro at different concentrations with the help of Cell Count Kit-8 (CCK-8 assay). The 400 µg/mL dosage of ZJSPs-1 inhibited HeLa cells (cervical cancer cells), and dosages of 164.6 and 87.1/µg/mL showed antiproliferative activity and apoptosis of cells for 24 and 48 h, respectively. The cell death increased with increased levels of dose and incubation time. Combining different methods with ultrasound gives more effective results than a single ultrasound treatment. Intake of Chinese dates in the form of functional foods or taking more of the polysaccharide as a supplement can prevent tumors. The honeycombed, multi-hole spherical structure of ZJSPs-1 particles was confirmed by scanning electron microscopy; these particles are produced by combining the fragmentation and erosion effects of USAE treatment. The primary mechanism by which this sonochemically modified ZJSPs-1 structure promoted anti-tumor activities on various cell lines might have been apoptosis [67]. Induction apoptosis is the primary method by which cells undergo shrinkage, condensed broken chromatin, and apoptotic bodies, with the concentration of these apoptotic bodies steadily rising [67].

In one study, the extraction of polysaccharides from Ziziphus jujuba cv. Muzao (ZJPs), using the water extraction method, achieved a purity of 95 %. These ZJPs were used on the cells of Caco-2 to analyze the cytotoxic effect. At concentrations of 25 to 800 µg/ml were given to the Caco-2 cells, but unfortunately, there was no cytotoxic effect; but at the dosage of 1000 µg/kg was given orally to the normal mice daily, and observed that these mice are physically healthy with no reduction in body weight and no deaths were recorded. This shows that ZSPs are very safe nutraceuticals and can treat alone or combined with other treatments [68].

In another similar study, the extraction of polysaccharides from Ziziphus jujuba cv. Goutouzao (ZJPs) used water extraction, and its extracted rate was 3.9 % (w/w). This extracted rate was further divided into concentrations to test the apoptosis of human colorectal carcinoma cells (LoVo) and macrophage cells (RAW 264.7). At the concentration of 400 µg/ml, there is apoptosis in cells of LoVo, which is 24 % after these cancer cells are incubated in the supernatant of RAW 264.7. This is one of the ways to treat the antiproliferative activity by using ZJP. This concludes that ZSPs can inhibit cancer by activating the immune cells in its pathway to treatment [69]. The in-vitro mechanism might involve cell cycle dispersion and the formation of reactive oxygenated species (ROS). These ZSPs can stimulate immune cells to decrease the RAW264.7 (macrophage cell line), inhibiting cancer cells by halting G0/G1 phases associated with ROS apoptosis. This type of mechanism is called immune dependent mechanism [69]. In a different study, the extract of polysaccharides from Ziziphus jujuba Mill was given to the rats
for 13 weeks daily via oral consumption at the concentration of 1000 mg/kg under in vivo conditions, resulting in decreased body weight, colon length, and protection against tumor necrosis. These polysaccharides are efficient in treating colitis and colorectal tumorigenesis; these polysaccharides can potentially restore gut microbes and act as a prebiotic [70].

3.3. Mango pomace

Likewise, mango pomace, a famous by-product generated during food processing, is rich in polysaccharides—non-traditional technologies, like USAE, extract polysaccharides, which benefit human consumption. In a study, dried mango pomace (MP) extract polysaccharides, which benefit human consumption and results in the formation of hydroxyl groups which aided in polysaccharide dissolution and diffusion. Increasing the material-to-water ratio directly affects MP yield. This ratio also improved the rate of solvent diffusion into cells and MP dissolution, but excess may result in polysaccharide extraction loss [71]. The anticancer activity of MPP was determined with the help of a CCK-8 kit in vitro, HepG2, MCF-7, A549, HeLa, A2780, HCT-116, and BGC-823 cells; these cells were treated with 25–1000 µg/ml. At 1000 µg/ml, MG-1, MG-2, and MG-3 showed significant inhibitory activities against the proliferation of HepG2, MCF-7, A549, HeLa, A2780, HCT-116, and BGC-823 cells in vitro [71]. Decrease cell proliferation via β-catenin, metalloproteinase-7 (MMP-7), MMP-9, and epithelial to mesenchymal transcription (EMT) [72].

3.4. Ginger

In one of the studies, extraction of polysaccharides from ginger (Zingiber officinale) was obtained by using the hot extraction method (HEC) and ultrasonic cell grinder extraction (UCGE). The optimum parameter for obtaining polysaccharides for HEC is 100 °C for 4 h in a water bath, and UCGE is 500 W – 30 min in an ice water bath. The yield for HEC was 11.74 ± 0.23 %, and for UCGE, 18.06 ± 0.05 %. This increase in the yield in the UCGE is because of the cavitation effect; burst bubbles release additional energy owing to shock waves, increasing the sulfate groups in the polysaccharides. Polysaccharides isolated from UCGE feature a unique structure of β-α-galactopyranose, a glycosidic linkage with more sulfate groups, showing anticancer activity against human colon cancer cells. This shows that the polysaccharides extracted from ginger by UCGE have a functional structure and can inhibit cancer cell lines [73]. The anti-tumor activity of polysaccharides extracted from UCGE is more effective than HEC polysaccharides at the dosage of 200 µg/ml on H1975 and Hela cell lines & at the inhibition rate of 150 µg/ml HCT116 and B16 [64]. In a similar work on the extraction of polysaccharides from Morinda citrifolia L. using a hot extraction method and ultrasound-assisted extraction, the yield was 11.13 % from USAE and 9.19 % in HWE. The optimal parameter value for both HWE and USAE is as follows: raw material to solvent ratio 1:41, water bath temperature 77.7 °C, time 117.6 min; 1:33.3, 78 °C, 81.7 min. The cell viability for USAE is more than HWE’s IC50 value, reduced from 45.45 % to 33.14 % by USAE polysaccharides on HepG2 cells [74]. Extraction from ginger results in cell shrinkage and chromosome condensation in HepG2 cells; this results in induction of apoptosis via the lysosomal mitochondrial axis where cathepsin-D is released before ROS generation and cytochrome release from mitochondria. This results in the protection of lipid peroxidation in liver tissue [75].

3.5. Blueberry wine residues

A novel extraction method named deep eutectic solvent (DESs) extraction in combination with USAE (380 W – 55 °C and 40 min) helped in the extraction of anthocyanins from blueberry wine residues to yield of 9.32 ± 0.08 mg/g (crude). The solvent utilized in the extraction procedure was DESs, and the water concentration in the DESs modified the physicochemical features of DESs, primarily viscosity and polarity, which improved the sonophysical effect and resulted in increased anthocyanin yield. Water substantially decreased the solvent’s sonophysical bonding, resulting in a rapid decrease in viscosity, which enhanced the sono physical rate of anthocyanins. A water concentration of 1 % to 3 % is desirable for anthocyanin production since too much water decreases yield. This DESs solvent is a mixture of choline chloride and 1,4-butanediol in a 1:3 ratio of DESs to water [76]. Further, the purification process obtained the purified component I named cyanidin-3-rutinoside, with a purity of 92.81 %. The crude extract and the component I were tested for anticancer activity with the help of flow cytometry analysis on HepG2 cells (cancer cells) and HL-7702 cells.

**Fig. 4.** Extraction of Ziziphus jujuba Mill. from Ruoqiangzao powder and separation of Ziziphus jujuba seeds polysaccharides-1 (ZJSPs-1) (Adapted from [67] and modified).
the effect is based on the time and dosage dependant. This crude extract of these bioactive substances. Another possible explanation for the acceptance of the drug by volunteered panelists and consumers is the free hydroxyl group at the 3-position in the flavylum moiety rather than replacements by diverse sugar moieties in the individual anthocyanins. Also, there is no toxic effect of crude extract and component I on HL-7702 cells, which indicates that this anthocyanin from the blueberry wine residue has adequate cell viability and apoptosis in cancer cells which can be used for further treatment [76]. In another study, the anthocyanin-rich fractions (ANRFs) were obtained from blueberry juice using the solid phase extraction method; the total anthocyanin content in 100 g of blueberry is 360.0 ± 0.76 mg. These ANRFs were further purified to perform bioactivity and were tested on three different cancer cell lines, which are A2780 (ovarian cancer), HeLa (cervical cancer), and B10F10 (murine melanoma). The cell viability of purified ANRFs decreased from 100 % to 52 %, 45.9 %, and 56 %, respectively, for the above cancer cell lines when the exposure time was 24 h. But the cervical cell lines showed sensitivity against blueberry ANRFs [77]. In another similar study, the extraction of anthocyanins from blueberry fruit by using aqueous and ethanol as a solvent. B16-F10 cells were treated with anthocyanins at 50 to 800 µg/ml concentrations. The inhibitory concentration value for this blueberry anthocyanin is 134.1 µg/ml. For cytotoxicity testing, normal mouse cells L929, which are commonly used for these types of tests, anthocyanins at the concentration of 12.5 to 800 µg/ml showed no cytotoxicity on this mouse cell line. These tests revealed that anthocyanins from blueberry extract showed potent cytotoxicity on B16-F10 cells. Doxorubicin was generally used as a positive control sample; this showed more cytotoxicity against B16-F10 and L929 cells than blueberry anthocyanin extract at the concentration range of 0.04 to 5.0 µg/ml [78]. The cellular mechanism was done using a flow cytometer; at the lower concentrations, there is a cell cycle arrest at G0/G1 phase and observed early apoptosis; further, an increment of concentration results in the late apoptosis and causes inhibition of the G2/M phase via apoptotic proteins [78]. Daily intake of blueberry powder (BB) in the diet of mice at percentages of 5 and 10 % results in decreasing of TNBC under in vivo conditions, no change in the overall health of mice, also there is decreasing in tumor volume at 5 % than 10 %. At 5 %, there are positive effects on breast maturation markers of progeny in pregnant rats. Along with anticancer properties, this blueberry powder intake acts as anti-inflammatory, antimetastatic activity. Different BB powder changes the gene related to cancer and inflammatory, developing liver and lymph metastases [79].

3.6. Raspberries

In a similar work, the extraction of anthocyanins from raspberries with the help of an ultrasound-assisted enzyme extraction method (UAEM) with the enzyme pectinase. The parameters were 30 min, 44 °C, 290 W, and 0.16 % of pectinase, respectively. The yield and efficiency from UAEM are 0.853 ± 0.009 mg/g and 84.75 ± 2.1 %, respectively. Increased pectinase concentration increases pectin decomposition in the cell wall of raspberry wine residue, improving cell membrane permeability to acidic cavitation and anthocyanin solubility. Furthermore, the combination of UAEM increased yield and efficiency by creating a cavitation effect that accelerated solvent penetration and anthocyanin dissolution. Increases in the breaking down of the cellular wall by cavitation pressure can explain the induction of these bioactive substances. Another possible explanation for these data is that hydroxyl radicals (OH−) created by ultrasound are added to the aromatic ring of phenolic substances that represented in Fig. 2 [80]. The total extraction, yield, and purification process are similar to the grape skin extraction procedure. After the purification process, the sample will undergo High-speed counter-current chromatography (HSCCC) to get highly purified anthocyanins named fraction I and fraction II. The purities are 93.46 % (cyanidin-3-glucoside) and 94.16 % (cyanidin-3-rutinoside) respectively. To get the anticancer activity of these fractions I and II, cell viability via 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The cells named A549 were treated with fractions I and II at 2.5 to 20.0 µM for 2 days. The results showed that cell viability drastically decreased with increasing infusion I and II concentrations; However, the cell viability of A549 cells treated with fraction II was lower than fraction I, and the anti-tumor effect of fraction II is better than that of fraction I; the pre-treatment of A549 cells with fraction II for 48 h shows the increasing level of intercellular reactive oxygen species (ROS), which inhibits the growth of the A549 cells. The apoptosis of these cells is more when treated with fraction II at different concentrations 2.5, 5.0, 10.0, 20.0 µM and the percentage apoptosis are (15.62 ± 0.36) %, (36.28 ± 0.41) %, (46.37 ± 0.68) %, and (54.72 ± 0.89) %, respectively. The percentage of apoptosis compared to the control group is 10.05, 31.18, 41.27, and 49.62 %, respectively, for the above concentration [81]. In one of the studies, the extraction of black raspberry extract (BRE) and its compounds was done by using ethanolic extraction, which consists of protocatechuic acid (PCA), one of the major metabolites in anthocyanins, inhibited the CYP3A4 activity in human hepatic microsomes only at concentrations of 50–100 µM but no sign of inhibition of 22Rv cells. This BRE inhibited the activity of 22Rv1 cells at low concentrations but not PCA. This BRE showed inhibition at high concentrations of 100–1000 µg/ml [81]. Anthocyanins influence the expression and activation of cell lines involved in various biological activities in the extracellular signal-regulated kinases (ERK) and mitogen-activated protein kinase (MAPK) pathways [82]. In some studies, black raspberry extract and anthocyanins-rich fractions were fed to the rats at 6.1 % for 35 weeks along with N-nitroso methyl benzylamine (N MBA), which decreased the esophagus tumor proinflammatory cytokine IL1 and enhanced the production of the anti-inflammatory cytokine IL10, IL12 these stimulate both cytolytic and natural killer cells [83].

3.7. Purple basil

In another study, the purple basil sinkencubin drink was treated with ultrasound to increase the bioactive compounds. The total phenolic content (TPC) was found to be 123.35 mg GAE (gallic acid equivalent)/L, and it was found that there is an 11.9 % increase in TPC by ultrasound than control. The extracted amount for Total Flavonoid Content (TFC) is 48.04 mg CE/L which is 12 % higher than the control (unsolicited). Similarly, the extract’s total antioxidant content (TAC) is 42.22 % and showed a 28 % increase concerning control. Additionally, cavitation-induced hydroxylation of the aromatic ring of phenolic compounds may enhance the quantity of compounds. Likewise, the extracted amount for Ascorbic Acid content (AAC) is 1.95 mg/100 ml. The overall acceptability of the drink by volunteered panelists and consumers is high because ultrasound treatment increased the aroma profiles through cavitation. The sonochemical effect produced by ultrasound increases aromatic rings of phenolic compounds via the sonophysical effects of acoustic cavitation. This increases the number of polyphenols and works as antioxidants [84]. The drink loaded with bioactive were analyzed for anticancer activity with the help of CCK-8 assay on human colon carcinoma cells (Caco-2); these cells were treated with different concentrations ranging from 250 – 400 µl/mL. The results showed a 75 % cell reduction in Caco-2 compared to the non-treated groups at the highest concentration of 400 µl/mL. The half-maximal inhibitory concentration (IC50) for ultrasound-treated purple basil drink is 276.6 µl/ml [84].

The study on the extraction of phytochemicals from dark purple basil blossoms (Ocimum basilicum L.) extract (DBPE) using a low-temperature hot water extraction method. The TPC and TFC from DBPE are 34.25
and 186.31 mg/g, respectively. For inhibition of growth and cell proliferation of MCF7 cells, these cells were treated with various concentrations of DPBE. At an inhibitory concentration of 250 μg/ml DPBE showed cell proliferation on MCF7 cells compared to untreated cells [85]. Increasing the ROS levels in mitochondria results in free radical attachment on membrane phospholipids; this will happen before the rising phase of the mitochondrial film, and this phase is irreversible in apoptosis, which triggers the caspase. For example, caspase-3 or 8 and 9 are the pro-apoptotic proteins from the beginning of intrinsic and extrinsic pathways; this protein inhibition plays a significant role in the induction of apoptosis [85]. In another similar study, the extraction of TPC and TFC from (Ocimum basilicum L.) leaves by using an ethanolic extraction process. The content of TPC and TFC were 226 ± 2 mg/g of extract and 213 ± 3 mg/g of extract, respectively. Along with ethanol extract, the hydro distillation of basil oil was carried out, revealing that this oil is rich in linalool 52 % and linalyl acetate 19.1 %. The ethanolic extract and oil from basil were treated against five human cancer cell lines (MCF7, MDA-MB-231 HeLa, PC3, and K562). The inhibition percentage was shown in LD50 values. Doxorubicin is used as positive control and obtained under the same experimental conditions. The anticancer activity of oil extract showed better treatment than ethanolic extract on cancer cell lines LD50 Values ranging from 300 to 1000 μg/ml [86].

3.8. Kokum

In a different study on USAE of polyphenols from kokum, at ultrasound intensity of 80 W cm⁻², 60 °C, methanol concentration of 75 %, and particle size of 0.1 to 0.25 mm, the TPC and TFC were found to be 698.4–732.76 mg gallic acid equivalent/g and 67.1–72.67 mg rutin equivalent/g. The effect on the extraction of polyphenols concentration depends on the intensity of the ultrasound, and as the intensity increases, so does the yield of polyphenols. This increase in polyphenol levels can be observed by increasing the sonochemical effect, but the continuous increase of intensity degrades the polyphenols, so it is recommended to use within the threshold level [87]. A dose of 60 μg/ml of optimal extract was used to detect anticancer properties in MCF-7 human breast cancer cells by invitro analysis; nearly 54 ± 2.1 % cell death was found in MCF-7 cells. The inhibitory concentration (IC₅₀) 60 μg/ml extract showed morphological change and effective cell death and was used for further studies [76]. The kokum is rich in various polyphenolic compounds like garcinol and can be used in non-invasive biomedicine because of extra hydroxyl groups present in it. In a similar study, using the soxhlet apparatus, a phytochemical test was done on methanol extraction from Garcinia indica (kokum) fruit. The TPC and TFC present in fruit extract are 0.34 gallic acid equivalent mg/g and 134.32 catechin equivalent (CE) μg/g, respectively. In vitro studies were done on HCT 116 cells and were treated with garcinia indica extract of 12.5 to 200 μg/ml. At the concentration of 200 μg/ml, the cell inhibition rate is 63.21 % [88]. In another study, the extraction of phytochemicals from Garcinia indica leaves (GIL) using the water (aqueous) extraction method. The amount of TPC and TFC present in GIL extract is 3.0 ± 0.47 mg GAE/g and 2.21 ± 0.33 mg Quercetin equivalent QE/g extract, respectively. In vitro analysis was done using the MTT assay method to get the influence of the extraction method on human kidney cancer cells like HEK-293 and A498. The cell viability was decreased with increasing the concentration of GIL extract. The cytotoxicity of above cell line A498 was identified at a concentration above 300 μM, but no cytotoxicity effect was observed in HEK 293 cells [89]. The activity method for the apoptosis or cell death by caspase actuated apoptosis in G0/G1 and S stages individually that aids in decreasing ROS levels [90]. In a new study, a polyphenol from kokum fruits was extracted and given in the form of encapsulated nanoparticles to the breast cancer mice with B16F10 melanoma tumor as in vivo study at the concentration of 50 to 100 μM via tail vein resulted in the active target of a tumor to muscle to blood reachability within 8 h of injection [91].

4. Antioxidant benefits of USAE bioactives from various food sources and food wastes

An antioxidant is a molecule that prevents the oxidation of other molecules and is defined as the substance which prevents or inhibits oxidative spoilage. An antioxidant in humans and food plays a crucial role as it scavenges reactive oxygen and reduces the oxidative process and the harmful effects of reactive oxygen species. Antioxidants prevent lipid peroxidation and the formation of secondary peroxidation products [104]. Reactive oxygen species in the human body lead to various chronic diseases, which can be prevented by antioxidants obtained from plants. Bioactive antioxidants include polyphenol, carotenoids, flavonoids, selenium, lipic acid, catechin, gallic acid, quercetin, and kaempferol [104–106] are identified as compounds that act against oxidation and specifically benefit on diseases and many conditions including cancer, aging, diabetes, cardiovascular, and neurological disorder, hypertension, Alzheimer diseases [106,107]. The flavonoids are associated with lowering the risk of fatal and nonfatal ischemic heart disease (IHD), total CVD, and cerebrovascular. Carotenoids are potent antioxidants that can scavenge the body’s free radicals and prevent CVD [105]. This antioxidant also can heal wounds that are caused by reactive oxygen species. Curcumin is one such polyphenolic compound that can reduce wounds.

The researchers gave the effects of curcumin which was being delivered by gelatin microspheres hydrogel on the skin of genetic diabetic rats, and on day 10, the results of epidermal thickness were obtained as 685.6 ± 13.3 μm, which was higher than the other two groups (432.9 ± 35.3 μm and 367.6 ± 7.36 μm) and found that curcumin reduces the wound size and improve the wound healing [105,108]. The leading cause of diabetes mellitus is impaired insulin secretion, associated with overstimulation or reduced stimulation of β-cell by chronic hyperglycemia or free fatty acid-induced ROS accumulation [109–111]. This leads to the subnormal expression of antioxidants in β-cell. So, antioxidants can alleviate diabetes. Exogenous triggers such as ultraviolet radiation (UVR) and visible light cause oxidative stress and cause hyperpigmentation (melanogenesis). This can be prevented by antioxidants not available in the superficial layer but the deeper basal skin.

The level of antioxidants is reduced during the aging process along with UVR exposure. The carotenoids protect against UVR exposure when taken as oral supplements for 4 weeks and irradiated for 24 h using a 150 W solar simulator, effectively reducing hyperpigmentation [112]. The presentation suggests that the imbalance in cellular reduction–oxidation leads to oxidative stress and subsequent development of diabetes due to β-cell dysfunction and insulin resistance. The antioxidant requires the delivery system to be incorporated into the body- a novel drug delivery system (NDDS). This includes Poly-ketals which are used for an intracellular delivery system. It can prevent oxidative stress, thereby reducing diabetes [111].

One of the novel techniques used in extracting these antioxidants is USAE. The extraction method involves the implosion of cavitation bubbles, which results in macro-mixing and micro-mixing of the medium. The efficacy of extraction of bioactive compounds from the food is achieved by high shear forces caused by cavitations in that medium. This leads to the fragmentation of the macromolecules, erosion, surface peeling, poration, and permeabilization of the cell wall, resulting in the extraction of the bioactive compounds. Compared with other conventional extraction methods, ultrasound-assisted extraction is highly reproducible, reduces the usage of solvents, purity of the products obtained in the reduced time, and no restriction of solvent and moisture content [113–115]. The bioactivity of antioxidant components in providing non-invasive health benefits is highlighted in the section below and Table 3 represents the antioxidant activity of USAE bioactives from various food products.
4.1. Annatto

In this study, a comparison between MAE (microwave-assisted extraction) and USAE and conventional treatments was made during the extraction of Bixin, polyphenols, and other antioxidant-rich compounds from annatto seeds. The extract of Bixin (80 %) containing highly conjugated molecule and other phenolic compounds with hydroxyl group capture the electrons and eliminate the singlet oxygen, thereby deactivating the excited triplet state of sensitizers and eliminating the free radicals showing more significant antioxidant activity [116]. Similarly, Fig. 5 represents the non-invasive biomedical antioxidant benefits of bioactives from USAE extracts.

Table 3
Antioxidant activity of various food products and its USAE bioactives.

| S. No | Food product       | Name of extracted compound | Yield            | Total antioxidant Activity | References |
|-------|--------------------|----------------------------|------------------|----------------------------|------------|
| 1     | Annatto            | Bixin, Polyphenols         | 0.67±0.066 %     | DPPH assay                 | [116]      |
|       |                    |                            | 2.85±0.0066 mg gallic acid/g | 1161.52± 28.96 μM Trolox/L seed |            |
|       |                    |                            |                  | FRAP assay                 |            |
|       |                    |                            |                  | 424.70±7 μM Trolox/L seed  |            |
|       |                    |                            |                  | ABTS assay                 |            |
|       |                    |                            |                  | 1035.65±189.517 μM Trolox/L seed |            |
| 2     | Green tea extract  | Gallic acid                | USAE-31.83±0.74 mg/g DW | TEAC assay                 | [119]      |
| 3     | Strawberry juice   | Epigallocatechin gallate   | USAE - 11.55±0.14 mg/g DW | DPPH assay                 | [125]      |
|       |                    | Phenols                    | TPC-95.76 mg GAE/g | USAE- 14.5%                |            |
|       |                    | Catechin                   | Catechin -7.52 mg/100 ml | TAA- 289.95 μmol/100ml     |            |
|       |                    | Gallic acid                | Gallic acid - 0.29 mg/100 ml | DPH assay-43.50%          |            |
|       |                    | Furalic acid               | Ellagic acid - 4.88 mg/100 ml | –                          |            |
| 4     | Orange peel        | Flavonoids                 | TPC-32.74 mg CE/g | I_{CC50} 251.56 μl          | [49]       |
|       |                    | Phenols                    | Optimal response | DPPH assay-190.75 mg GAE/100 ml |            |
|       |                    |                            | Optimal phenolics | ABTS assay                 |            |
|       |                    |                            |                   | I_{CC50} 995.57 μl         |            |
| 5     | Whey protein       | β-Lactoglobulin            | –                | ABTS assay                 | [133]      |
| 6     | Sesame bran        | Phenols                    | TPC- 6.03 mg GAE/g | ABTS assay-42.9 μmol TE/g   | [136]      |
| 7     | Green propolis     | Phenolic compound          | TPC-533.9 mg GAE/g | ABTS assay-13412.1 μmol TEAC/g | [139]      |
|       |                    | Artepillin C               | Artepillin C - 807.6 ± 57.7 mg/g, | DPPH assay- 3524 μmol TEAC/g |            |
|       |                    | p-coumaric                 | p-coumaric - 45.6 ± 0.2 mg/g | ORAC assay                 |            |
| 8     | Sweet potato protein | Peptide (3 KDa)          | Degree of hydrolysis (DH %): | ORAC assay                 |            |
|       |                    |                            | Alcalase - 43.91 ± 0.12 | Fe2+ (ferrous) chelating activity | [143]      |
|       |                    |                            | Flavourzyme (peptidase) - 35.26 ± 0.92 | Alcalase-98.448±0.05%, |            |
|       |                    |                            | Combined - 50.98 ± 0.66 | flavourzyme-73.93±0.22%, |            |
|       |                    |                            |                   | combined-98.59±0.09%        |            |
|       |                    |                            |                   | O-H (hydroxyl) scavenging activity |            |
|       |                    |                            |                   | ascorbic acid-67.11±0.38%, |            |
|       |                    |                            |                   | flavourzyme-57.04±0.82%     |            |
|       |                    |                            |                   | combined-60.06±0.09%        |            |
| 9     | Onions             | Flavonoids                 | Total flavanols - 8.78 ± 0.03 mg/g | ABTS assay- 146.4%          | [144]      |
|       |                    | Mannose                    | Mannose-17.1%     | DPPH method                 | [145]      |
|       | Fungus             | Rhamnose                   | Rhamnose-9.3%     | 80.80%, I_{CC50}1.45 mg/mlO-H |            |
|       | Ganoderma Lucidum | Glucose                    | Glucose-50.2%     | (hydroxyl) scavenging activity |            |
|       | polysaccharides    | Galactose                  | Galactose-16.4%   | ascalose-67.11±0.38%, |            |
|       |                    | arabinose                 | Arabinose-8%      | flavourzyme-57.04±0.82%     |            |
| 11    | Kiwi fruit juice   | Phenolics                  | TPC- 120.18 GAE/mg | FRAP ASSAY- 65.67%          | [146]      |
|       |                    | Flavonoids                 | TPC- 105.56 GAE/mg | DPPH - 45.50%               |            |
|       |                    | Ascorbic acid              | Ascorbic acid content - 18.59 mg/100 ml | TA- 249.07% |            |
| 12    | Pomegranate peel   | Phenols                    | TPC- 177.54 mg GAE/g | DPPH ASSAY- 81.67%          | [147]      |
|       |                    | Flavonoids                 | TPC- 35.71 mg QE/g | I_{CC50} 0.365 mg/ml       |            |
|       |                    | Anthocyanin                | DPPH ASSAY- 40.30% | ABTS- 76.50 %, I_{CC50} 0.295 mg/ml |            |
| 13    | Brown seaweed      | Phenols                    | TPC-572.3 ± 3.2 mg GAE/g | DPPH ASSAY- 146.4%          | [148]      |
|       |                    | Flavonoids                 | TPC- 281.0 ± 1.7 mg QE/g | FRAP ASSAY- 86.7%          |            |
|       |                    | Phlorotannins              | TPC-476.3 ± 2.2 mg PE/g | –                          |            |

TPC- Total phenolic content, TFC- Total flavonoid content, TPhC- Total phlorotannins content, TAA- total antioxidant activity, ORAC assay- oxygen radical absorbance capacity assay, DPPH assay- 2,2-diphenyl-2-picrylhydrazyl hydrate assay, FRAP assay-ferric reducing-antioxidant power assay, ABTS assay- 2,2’-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid, TEAC assay - Trolox equivalent antioxidant capacity, IC50- half maximal inhibitory concentration, GAE- gallic acid equivalents, QE- quercetin equivalents, PE-phlorotannins equivalent, TE- Trolox equivalent, DW- distilled water.
value of $1035.652 \pm 189.517 \mu\text{M Trolox/L}$ of extract, which was the highest of all. In FRAP (ferric reducing antioxidant power), UAE shows $424.700 \pm 7.00 \mu\text{M Trolox/L}$ of extract, whereas, in MAE, it was $316.37 \pm 10 \mu\text{M Trolox/L}$, which was near to UAE extract. In DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) method, UAE gives the value of $1161.524 \pm 28.938 \mu\text{M Trolox/L}$ of extract, whereas MAE gives $1043.90 \pm 50 \mu\text{M Trolox/L}$ of extract. Thus, UAE extraction gives the highest of all methods, significantly showing higher antioxidant activity. Overall, the MAE leads to the denaturation of a bioactive compound due to heating, unlike the non-thermal USAE process. The polyphenols from annatto seeds were extracted by the conventional method with ethanol in the ratio of 1:2 (seed to solvent). The polyphenol obtained from the conventional method was found to be $0.343 \pm 0.031 \text{mg AG/g seed}$, and the bixin percentage was about $0.165 \pm 0.002$. The antioxidant activity of polyphenols were found to be $174.782 \pm 8.700 \mu\text{M Trolox/L}$ extract by ABTS method, $127.033 \pm 2.517 \mu\text{M Trolox/L}$ extract by FRAP method, and $81.048 \pm 5.774 \mu\text{M Trolox/L}$ by DPPH method. Since Bixin is soluble in basic pH; in contrast, polyphenol is soluble in acidic pH; the ideal conditions for obtaining the most outstanding amounts of Bixin and polyphenols are pH 7.0 with a solvent concentration of 96 percent for 30 min. The residency period of cavitation bubbles in contact with seeds, which readily release the bioactive component, is connected to the extraction time, making it essential [116].

An in vivo study is carried out using nanoparticles of Bixin to treat acute lung inflammation in mice, which is induced by exposure to cigarette smoke. Bixin’s antioxidant and antichemotactic potential prevented the increase in superoxide anion and total bronchoalveolar leukocyte levels in mice exposed to CS. The Bixin-like compounds, which are poorly soluble, were dispersed using the correct carrier material like poloxamer to administer them orally. Thus, the bioactive Bixin can be used as a therapeutic tool for alleviating lung diseases like chronic obstructive pulmonary disease (COPD) [117].

Similarly, in a different study, the bioactive Bixin alleviates renal fibrosis, a degenerative disease that leads to end-stage renal failure. In this study, the condition of renal fibrosis, including oxidative stress, inflammation, and fibrosis, was induced in mice by CCl$_4$ and were treated with 100–200 mg/kg of Bixin. In the CCl$_4$ group, Bixin significantly reduced kidney damage and tubulointerstitial and glomerular lesions score. Bixin treatment also reduced collagen deposition in the CCl$_4$ group’s kidneys. It also significantly reduced the expression of fibrotic markers α-smooth muscle actin (α-SMA) and collagen in the kidneys of CCl$_4$-treated animals. In addition, the CCl$_4$ group had significantly greater levels of ROS and malondialdehyde, whereas Bixin therapy significantly reduced these renal oxidative stress markers. Furthermore, the activities of superoxide dismutase, catalase, and glutathione peroxidase were reduced by 39.8 %, 35.6 %, and 28.6 %, respectively, in the CCl$_4$ group. Likewise, the inflammatory cytokines were decreased after Bixin supplementation and thus inhibited CCl$_4$-induced renal fibrosis and inflammation by regulating the Nrf2/TLR4/MyD88 and PPAR-γ/TGF-β1/Smad3 pathways; thus, Bixin can be used for alleviating renal fibrosis [118]. Bixin’s comprehensive mechanism on CCl$_4$ produced inflammation, oxidative stress, fibrosis, and reduced kidney damage by lowering blood creatinine, urea, and uric acid levels. Similarly, Bixin improved CCl$_4$-induced inflammation in the kidneys by lowering TNF-α and IL-1β levels. It reduced oxidative stress by boosting Malondialdehyde (MDA) levels and activating superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX). It also boosted Peroxisome proliferator-activated receptor gamma (PPAR-γ), NAD(P)H dehydrogenase [quinone] 1 (NQO1), Heme oxygenase-1 (HO-1), and nuclear factor erythroid 2-related factor 2 (Nrf2) expression in mice kidneys by blocking toll-like receptor (TLR4), myeloid differentiation (MyD88), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), transforming growth factor beta (TGF-β), and mothers against decapentaplegic homolog 3 (Smad3) activation [118].

4.2. Green tea

Consumption of green tea significantly reduces several chronic diseases, and the antioxidants are responsible for this effect, especially the catechins and tannins. Usually, the enzyme tannase involves hydrolyzing the bond in gallic acid in tannins and reduces the compound by breaking ester bonds, increasing gallic acid and thus the antioxidant activity. So, in this study by Xu et al [119], combining enzyme tannase and ultrasound treatment increased the gallic acid content as it hydrolyses the tannins. Here, the ultrasound enhanced the release of phenolic compounds and increased the enzyme action rate, improving the green tea’s antioxidant activity. The content of gallic acid in terms of antioxidant capacities of UST (Ultrasound treated) and TAN (tannase enzyme)
is given in percentages (28.70 % and 26.00 %, respectively). Also, this study investigated the reduction of the content of epigallocatechin gallate in green tea extract into gallic acid and its non-invasive health benefit by reducing free radicals by acting as a potent antioxidant. The values for different antioxidants for green tea extract under UAE included gallic acid- 31.83 ± 0.74 mg/g DW, Epicatechin- 1.96 ± 0.31 mg/g DW, Epigallocatechin-2.02 ± 0.73 mg/g DW, Caffeine- 17.00 ± 0.63 mg/g DW, Ellagic acid- 1.31 ± 0.04 mg/g DW, Epigallocatechin gallate- 0.16 ± 0.06 mg/g DW [107]. This extract helps in prevention of diseases by quenching of free radicals because of phenolic structure which is represented in Fig. 2.

More variety of teas could also be employed with these methods to improve antioxidant activity and studies can be performed in vitro/in vivo to realize the health benefits.

The bioactive compound in green tea was extracted by conventional method (hot water extraction), which includes epigallocatechin gallate (3.810 ± 0.26 g/100 g), epigallocatechin (2.290 ± 0.11 g/100 g), epicatechin gallate (0.649 ± 0.03 g/100 g), epicatechin (0.412 ± 0.02 g/100 g) [120]. The organic green tea’s catechin and polyphenols were extracted using spray-dried hot water. The polyphenol content was about 179.01 ± 4.15 µmol GAE/100 mg. The antioxidant activity of these organic green tea was obtained using DPPH and ABTS methods with 48.9 % and 85 % of antioxidant activity, respectively. The anti-oxidant values were 4.84 ± 0.2/10 mg in the DPPH assay and 8.42 ± 0.3/10 mg in the ABTS assay. The concentration of tannase was set at 1 mg/ml with an optimal pH of 4.62, ultrasound temperature of 44.12 °C, and 12.17 min at 360 W of ultrasound power since the enzyme tannase was employed to improve extraction. The enzyme and ultrasound improved green tea’s antioxidant activity, which works together to promote the bioconversion of bioactive components in green tea extracts [121]. The mechanisms through which tea polyphenols create antioxidant benefits include the following processes: an increase in antioxidant enzyme activity, suppression of lipid peroxidation, free radical scavenging in conjunction with other nutrients, and oxidation-reduction via metal ion chelation [122].

The polyphenol-rich extracts of green tea mitigate the aflatoxin B1-induced pulmonary aflatoxicosis in albino rats by its antioxidant, anti-inflammatory, and cytoprotective agents. The inflammatory cytokines and oxidative stress indicators were dramatically reduced when green tea extract of 30 mg/kg/day for 8 days was given to aflatoxicosis-induced rats [123]. Tea polyphenols administered at 300 mg/kg for 12 weeks for ovariectomized rats with Alzheimer’s disease improved the condition of aging-related memory decline by modulating the balance of hexosamine biosynthetic pathway-dependent glycosylation and Tau phosphorylation and the mitochondrial structure. Moreover, via modulating the glycolysis and oxidative phosphorylation of glucose, the epigallocatechin gallate intervention can protect PC12 cells from Ap1-42-induced damage [124]. Hence the nutraceutical tea polyphenols can be used for alleviating conditions like memory decline and aflatoxicosis.

4.3. Strawberries

In another study, the ultrasound treatment on strawberry juice significantly improved the color, total phenols, ascorbic acid, flavonoids, and antioxidant activity. The thermal processing of the juice led to the degradation of this bioactive compound; however, usage of the UAEA readily preserved the bioactive compounds and their availability. The comparison of antioxidant contents in juice under different treatments (conventional and ultrasound) was made on total phenols (TP), total flavonoids (TF), and DPPH values. The total phenols increased in time for ultrasound-treated samples from 57.60 mg GAE/100 ml to 95.76 mg GAE/100 ml (control to 12 min UST). The flavonoid content increased by 80 % compared to the control (from 18.20 mg CE/100 ml to 32.74 mg CE/100 ml). The total antioxidant activity was about 289.95 µmol/100 ml, about a 51.6 % increase from the original content of 191.30µ/100 ml, thereby increasing its antioxidant content. The highest DPPH inhibition was obtained for US 12 min, which was 43.50 % compared to control (31.50 %). Likewise, the catechins obtained from the conventional method were 4.05 mg GAE/100 ml but ultrasound treatment for 12 min was 11.57 mg GAE/100 ml. The ultrasound process can thus be employed to make functional foods as strawberry juice does not show much change in color and microstructure of the strawberries during the extraction process. The hydroxyl group in polyphenols increased with the ultrasound processing duration (0 to 12 min), and the ultrasound processing was stopped in the sixteenth minute, using an ultrasonic processor with a probe at a frequency of 20 kHz and 400 W. The fundamental cause is an increase in antioxidant activity from extracted strawberry juice mediated by the attachment of hydroxyl radicals (OH-) created by sonochemical action connected to the aromatic ring of phenolic compounds [125].

Initially, strawberry juice was smashed with double distilled water in the ratio of 1:2, which was the conventional method of extracting juice. The total phenols and flavonoid concentrations were 57.60 ± 0.56 mg GAE/100 ml and 18.20 ± 0.06 mg CE/100 ml. The antioxidant activity of the conventionally prepared strawberry juice was found to be 191.30 ± 1.59 µmol/100 ml, and the DPPH assay gives the % inhibition of 31.50 ± 0.11. This clearly shows that UAE extraction gives higher polyphenols and flavonoids and thus has higher antioxidant activity, the beneficiary effect of antioxidant is due to phenolic rings and multiple hydroxyl groups. Thus, US-treated antioxidant-rich strawberry juices can provide non-invasive biomedical benefits such as aging delay and cancer resistance [125].

In a study, dietary polyphenols from strawberries reduce aging in rat models because of their antioxidant properties. The same study looked at the impact of strawberry consumption on oxidative damage indicators and aging-related declines in the functioning of mitochondria and biogenesis for 8 weeks. Strawberry supplementation increased antioxidant enzyme activity, mitochondrial biomass, and function and decreased intracellular ROS levels and protein, lipid, and DNA damage markers. Thus, antioxidants mitigate oxidative stress in older rats, activate the AMPK signaling pathway, and slow the aging process [126]. Inflammation, oxidative stress, cartilage deterioration, and joint space narrowing are all associated with osteoarthritis pain symptoms. As a result, it is logical to suggest that antioxidant supplements may be beneficial. Strawberries with high antioxidants, mainly from polyphenols, reduce the symptoms of osteoarthritis on the knees of obese adults. Interleukin (IL)-6, IL-1, and matrix metalloproteinase (MMP)-3 were considerably lower in serum indicators of inflammation and cartilage degeneration after strawberry freeze-dried beverage intake for 12 weeks versus control treatment. Strawberry supplementation effectively reduces reactive oxygen species (ROS) by lowering malondialdehyde formation, protecting low-density lipoprotein (LDL) from oxidizing, and preventing mononuclear blood cells from higher DNA mutations, a feasible and essential strategy [127].

The strawberry supplementation significantly reduced constant, intermittent, and overall pain. The medication did not affect the blood’s C-reactive protein (CRP), nitrite, glucose, or lipid profiles. In obese persons with established knee osteoarthritis, dietary strawberries may have significant analgesic and anti-inflammatory effects [128].

4.4. Orange peels

The orange peel contains bioactive compounds such as phenolics, aldehydes, terpenes, alcohol, and esters, promoting health benefits and the prevention of diseases. The essential oil usually possesses antimicrobial and antioxidant properties, primarily due to the 90 % of limonene, a terpene. The more beneficial effect of essential oil only depends on the extraction process. In this study, two optimal extraction conditions for bitter orange peel extracts were given as OP (optimal phenolics) and OR (optimal response). OP gives the maximum TPC of 190.75 mg GAE/100 ml compared to OR (108.33 mg GAE/100 ml). The redox characteristics of phenolics groups contribute to their high antioxidant
action. IC₅₀ values for inhibiting microorganisms from extracted bioactive compounds for OP and OR were 218.14 ± 4.80 μL and 263.28 ± 10.32 μL, respectively, against three types of microorganisms, *Bacillus cereus*, *Staphylococcus aureus*, and *E. coli* which was higher for OR. Here ultrasonic extraction was taken to reduce the extraction time compared with hydro distillation. The cavitation process, which causes the tumefaction of cells, the collapse of cell walls, high diffusion rates across the wall, and the penetration of the cell components, also caused the TPC to increase with the increase in ultrasonic time at shorter hydro distillation extraction time. TPC, however, was reduced as the hydro distillation extraction time was increased at a longer ultrasonic time. This might be due to the sonophysical effect that heat destroyed phenolic compounds after being diffused by ultrasound [49].

The conventional method of extracting polyphenols using solid–liquid extraction was done with DES (deep eutectic solvent), where choline chloride-based DES with glycerol and ethylene glycol. This method gives the total phenolic compound 5.84 mg GAE/g orange peel using DES with ethylene glycol. Polyphenols such as ferulic acid, p-coumaric acid, and gallic acid. The antioxidant capacity of the polyphenolic extracts with choline chloride-based DES with glycerol was found to be 44.8 ± 1.9 μg/mL (IC50 value). UAE extraction shows higher TPC and antioxidant activity than DES-based solid–liquid extraction [129]. Primary dysmenorrhea, one of the most frequent gynecologic illnesses, has affected women of reproductive age in their daily lives and jobs. During primary dysmenorrhea, the women experience intense spastic pain. The findings demonstrated that CEOs might improve antioxidant status markers such as total antioxidant capacity, superoxide dismutase, catalase, and glutathione, as well as lower malondialdehyde and inducible nitric oxide synthase levels and the prostaglandins ratio of PGE₂/PGF₂α in the estradiol benzoate and oxytocin-induced rat uterus, hence alleviating the writhing pain reaction. Essential oils of sweet orange and bergamot had a more substantial effect than those of other CEOs. Thus, citrus essential oils could effectively suppress oxidative stress and prostaglandin-induced uterine contractions, and the condition of primary dysmenorrhea further non-invasively by using such limonene bioactive [130]. In another in vivo study, limonene and flavonoids from citrus peel wastes have shown protection from the lymphoma of Dalton’s Lymphoma Ascites (DLA) cells. Thus, citrus peels can be valorized into bioactives like limonene and used as a natural, non-invasive medicinal remedy to treat cancer [131]. Similarly, the components such as limonene and others, including myrcene, α-pinene, β-pinene, phellandrene, geraniol, and geranial found in citrus essential oils, we’re able to reverse the increase of the PGE₂/PGF₂α ratio in RBL95-2 cells, i.e., in the human endometrial carcinoma cells [130]. Fe (II) chelation and hydroxyl radical (OH•) scavenging are proposed mechanisms by which phenolic extracts protect the organs. Because phenolic extracts demonstrated more Fe (II) chelating capacity than OH• scavenging ability, Fe (II) chelation may be the dominant mechanism by which phenolics protect the cell membrane from Fe (II)-induced lipid peroxidation [132].

4.5. β-lactoglobulin

The property of β-lactoglobulin in providing the antioxidant property is due to the formation of peptide fragments by the enzymatic hydrolysis due to the proteolytic enzymes. In a study, Shuang Ma et al [133], obtained a broad negative absorption peak at 218 nm due to an antiparallel β-sheet. The ultrasound treatment enhances the α-helix and β-sheets structure of β-lactoglobulin. The hydrolysis by ultrasound shows a higher amount of α-helix and β-sheets. The native β-lactoglobulin have shown ABTS radical scavenging of 30.60 % at 10 mg/L but increased to 60.82 ± 0.23 % at 10 mg/L with ultrasound. This was mainly due to the breakage of β-lactoglobulin, which increased its surface area, providing more sites for binding the free radicals and improving activity. This ability is due to the presence of phenolic hydroxyl group that helps in the antioxidant activity. While treated with enzyme pepsin alone, radical scavenging was 50.82 % at 10 mg/L; however, after ultrasound treatment, the pepsin activity increased from 56.36 to 87.43 %. Then with enzyme trypsin alone, it was 87.73 %, and with combined ultrasound and trypsin, it was around 90.58 % at 10 mg/L. This shows that enzyme hydrolysis, along with ultrasound, enhances the activity of peptides of β-lactoglobulin as an antioxidant. CaCO₂-2 cell model was a human colon adenocarcinoma cell line with microvilli, similar to intestinal epithelial cells with microvilli. Its cell viability was determined with an MTS assay. Here H₂O₂ – an induced CaCO₂-2 cell model was made to establish the protection against oxidative stress by the effect of ultrasound and enzymatic treatment of β-lactoglobulin. The cell viability was significantly reduced with exposure to 0.6 mM H₂O₂, leading to cell damage. The β-lactoglobulin at a concentration of 50 mg/ml showed no cytotoxic effect, but at the concentration of 100 mg/ml, the cell viability of all samples was improved, especially when treated with ultrasound increased from 80.06 ± 1.33 % to 91.08 ± 0.43 %. At 800 mg/ml concentration, the maximum cell viability of β-lactoglobulin was found to be 99.19 ± 0.64 %. This showed that β-lactoglobulin exhibited the cytotoxicity effect on CaCO₂-2 cells induced by H₂O₂. So, such whey protein hydrolysate-rich foods treated with ultrasound can produce enhanced bioactive, giving biomedical benefits to consumers. Here, the native β-lactoglobulin showed an antioxidant of 30.60 ± 0.13 % by the ABTS method in the conventional method. The β-lactoglobulin solution was treated for 15 min with a probe sonicator at a frequency of 20 kHz and an intensity of 120 W/cm². By exposing the hydrophobic amino acids previously concealed in the hydrophobic core, the sonochemical effect of ultrasonic waves alters the structure of the β-lactoglobulin, which causes pepsin/trypsin to cleave and produce tiny peptides. The susceptibility of β-lactoglobulin during in vitro stomach digestion is improved by ultrasound. It showed that ultrasonic pretreatment might significantly increase β-lactoglobulin antioxidant activity during in vitro digestion, which was attributable to an increase in β-lactoglobulin susceptibility to forming many small-molecule antioxidant peptides [133]. In vitro digestion of β-lactoglobulin binding with IgG/IgE and its anti-oxidant activity, their structure influenced by ultrasound. Native β-lactoglobulin can cause allergenicity due to its resistance to gastric digestion. But ultrasound followed by gastric digestion increases the small peptide with a decrease in immunogenicity [134]. Antioxidants propose two fundamental ways of preventing oxidation: single electron transfer (SET) and hydrogen atom transfer (HAT) (HAT). Plasma’s ferric reducing capability is an excellent SET-based analytical tool (FRAP). Fe (III) forms a compound with tripyridyltriazine (TPTZ) and oxidizes it in this method [135].

As a result, the antioxidant gives the Fe(III)-TPTZ complex a single electron. The subsequent drop in absorbance is due to the ability of the electron-donating antioxidants to diminish. The oxygen radical absorbance capacity (ORAC) approach is a standard HAT method that relies on a radical initiator to generate peroxyl radicals (ROO). When the ROO interacts with a fluorescent probe, its fluorescence decays. The antioxidant neutralizes the ROO by transferring a hydrogen atom to it, blocking the interaction between the ROO and the fluorescent probe. As a result, the more the antioxidative activity, the faster the fluorescence disappears [135].

4.6. Sesame bran

The sesame bran contains 15 % protein, and its extraction was enhanced by combined methods of enzymatic and ultrasound treatment than by conventional methods. Alcalase (proteolytic enzyme) was combined with ultrasound and gave a higher amount of TPC (Total phenolic compound) than with enzyme viscosome L (cellulolytic enzyme). The protein extraction with alkaline treatment gives the value of 25 %, which was less when compared with enzymes alone, UAE, and combined. The obtained values were alcalase-79.3 %, viscosome L-41.7 %, UAE alone-59.8 %, and combined enzyme and UAE treated-87.9 %. TPC of enzyme- viscosome L, alcalase, ultrasound alone, and ultrasound-
assisted enzymatic extraction give the value of 3.80, 6.61, 3.82, and 6.03 GAE/g, respectively. ACaPPH (Antioxidant capacity) (2,2-Diphenyl-1-picrylhydraz and AABTS (2,2' Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) values were 1.24–3.55 and 37.9–42.3 μmol TE/g respectively. Enzymatic and UAE methods increased the protein yields between 39.8 and 58.5 percent and the antioxidant activity compared to alkaline extraction methods, and the optimum conditions were ultrasound energy (528–836 W), a frequency of 35 kHz, and temperatures ranging from 25 to 55 °C. The antioxidant activity is due to the presence of phenolic compounds which will add post extraction process. The enzyme Alcalase was more effective in extraction than viscozyme L. SEM analysis results in bran deformation, leading to the highest protein yields. The conventional method of extracting sesame bran polyphenols using the alkaline extraction method of extraction sesame bran was mixed with deionized water in a ratio of 1:10 (w/v). Then it was centrifuged to obtain the filtrate. The total phenol content obtained from this type of extraction was 3.8 GAE/g; thus, the antioxidant activity. According to the findings, the recovery of protein and polyphenols from sesame bran was made more accessible by ultrasound-assisted extraction at a high ultrasound power. The sonophysical effect of ultrasonic waves, which creates a larger surface area for interaction between the solid matrix and liquid solvent, may help to explain this. Similarly, it is claimed that ultrasound’s high temperatures and shock waves break molecular and cell wall bonds, accelerate sonochemical effect through cavitation, and improve protein and phenolic extraction [136]. The proteins play an essential role in children’s growth and can be used in milk modifiers [137]. Since the extract components may scavenge free radicals via electron- or hydrogen-donating routes, they should be able to prevent the start of damaging hydroxyl radical responses in sensitive matrices like cellular membranes. This shows the sample’s ability to degrade different free radicals in different programs, hinting that they could be beneficial clinical agents for addressing clinical damage caused by radicals [138].

4.7. Propolis

In the study on USAE extraction of propolis, the conventional extraction process requires extended time, up to 12 h, to first separate it from raw materials and then phenolic compounds. In UAE extraction, time was kept at 20 min, providing a better yield of phenolic and antioxidant activity. Using the ABTS method, the antioxidant value was 13412.1 μmol TEAC/g. The phenolic compounds such as p-coumaric were found to be 45.6 mg/g of sample, and artepillin C was 807.6 mg artepillin C/g. There was no significant difference between synthetic antioxidants and green propolis. Its extract contains a higher amount of rich artepillin C, which shows similar results as tertiary butyl hydroxy cinnamic acid derivate have benefits in treating inflammation, viral disease, and tumor in cell culture and animal models [141]. The mechanism might be that Art-C might exhibit antioxidant activity by raising the potential of endogenous proteins such as reduced glutathione (GSH), glutathione reductase (GR), melatonin (MEL), glutathione peroxidase (GP), superoxide dismutase (SOD), and catalase (CAT), which decreases pro-oxidative and nitrosative compounds that cause cellular damage [142].

5. Cardiovascular health and antidiabetic benefits of USAE bioactives from various food sources and food wastes

Cardiovascular health indicates the health of the heart and blood vessels. Cardiovascular diseases are a group of abnormalities related to the heart and blood vessels, such as coronary heart disease, heart failure, heart arrhythmia, and heart valve problems. There are various reasons for cardiovascular diseases, out of which nutrition and diet intake play a significant role. Some foods are cardioprotective, and some foods also risk cardiovascular health [149]. Some of the USAE bioactive and their role in the improvement of cardiovascular health are provided below.

5.1. Ash gourd

Non-enzymatic glycation of proteins results in the formation of advanced glycated end products (AGEs), which have a negative impact on different health conditions like neurodegenerative diseases, diabetes, cardiovascular diseases, and inflammation. Studies report that the formation of AGEs is also linked to chronic illnesses like cardiovascular health, Alzheimer’s, etc. [150]. In a study, the polysaccharides from Benincasa hispida (PBH), a vegetable, were extracted using ultrasonic treatments and were studied to investigate their antiglycation activity. The ultrasonic power increased the anti-glycation activity by 35 ± 0.5 % at 50 °C. High acceleration, multistage effect breaking, mixing, the increased material sonochemical effect that increased the target component into the solvent and encouraged extraction [151]. The anti-glycation activity reported in the ultrasound extracted compounds is indirectly linked to the enhancement of cardiovascular health. As the AGEs are generated from the thermal reactions (Browning & Maillard) and are formed cause of the heating of the foods, a step which can be skipped in ultrasonic extraction [152]. The extraction of polysaccharides (water soluble) from hot aqueous extract of Benincasa hispida was investigated by Kuiwu Wang et al. The polysaccharides were mainly D- galactose and D- glucose, with a yield of 12.08 % from dry powder [153]. In a study, when the HCl-deproteinizing Chinese watermelon polysaccharides concentration was 20 mg/ml, the superoxide anions scavenging ratio was found to be79 percent. It is also confirmed that they can act as a potent antioxidant and thus possibly inhibit lipid peroxidation in humans. Thus, plants high in antioxidant polysaccharides, such as herbal Benincasa hispida (ash gourd or wax gourd) polysaccharides, are effective at removing reactive oxygen species like superoxide ions, hydrogen peroxide, and hydroxyl radicals from the fatty acids circulating in human blood, have been linked to the prevention of heart disease, cancer, and neurodegenerative disorders. As a result, herbal polysaccharides with antioxidant potential and robust scavenging ability have been proposed as a nutraceutical component with non-enzymatic medical advantages in pharmaceutical and food products. High blood pressure, lipid problems, high LDL (bad) cholesterol, high triglycerides, low HDL (good) cholesterol, smoking, obesity, lack of physical activity, and poorly controlled diabetes make people with diabetes two to four times more likely to develop cardiovascular disease [154,155] The method by which these fruit extracts exert their anti-diabetic effects might be via stimulating insulin release from residual pancreatic -cells or its release from the bound form [155].

Thus, in a study, ash gourd (Benincasa hispida) was provided in a
diet for 90 days with curry leaves to study the lipid profiles of diabetic patients, which could affect heart health. Before supplementation with diet, the diabetic patients’ mean total cholesterol level was 274.3 mg/dl, but after three months of salad supplementation, it had dropped significantly to 222.2 mg/dl. Likewise, before therapy, the mean HDL cholesterol level was 66.5 mg/dl, but after supplementation, it had climbed to 79.5 mg/dl. Similarly, the mean value of LDL cholesterol before supplementation was 168.3 mg/dl; after supplementation, it had significantly fallen to 114.4 mg/dl. Also, the mean value of VLDL cholesterol was 39.3 mg/dl, but after supplementation, it dropped to 28.3 mg/dl, and the mean triglyceride level was 196.4 mg/dl before supplementation and decreased to 141.1 mg/dl after supplementation, with a significant reduction. Thus, the overall lipid profile of diabetes patients showed an improvement after supplementation, which would benefit heart health. This benefit may probably be due to antioxidants present in the supplements, which have reduced the lipid peroxidation in the blood [156].

5.2. Ziziphus varieties

The *Ziziphus lotus* HGMR inhibitory activity (anti-lipidemic activity) was evaluated at a concentration of 100 µg/ml, and the ultrasound extracted content showed an activity of 45.41 %, which is higher when compared to that of conventional extraction methods [157,158]. Kim et al. have shown the improvement of the serum lipid profile of Sprague Dawley male rats upon consumption of water-based extracts of Jujuba seeds for 10 days, and thus these extracts can reduce hyperlipidemia and alleviate the related cardiovascular diseases [159]. According to a recent study, consuming Ziziphus jujube regularly can help persons with Type 2 diabetes improve their lipid profiles and blood glucose levels. In this randomized controlled clinical trial, 48 individuals between the ages of 30 and 65 were assigned to one of two groups: intervention (n = 24) or control (n = 24). The intervention group received 30 g of Ziziphus jujube every day for 12 weeks. After the intervention, the fasting plasma glucose (FGP), triglycerides (TGs), total cholesterol (TC), and low-density lipoprotein-cholesterol (LDL-C) all dropped significantly in the Ziziphus jujube group compared to baseline, which was –11.36 %, –13.59 %, –7.46 %, –7.65 %, respectively and which in turn improved the cardiometabolic factors [160]. Catalase, Glutathione disulfide (GSSG)-Red, and glutathione peroxidase (GSHPx) are all essential oxidative stress indicators. The findings that streptozotocin-induced diabetes is associated with a considerable increase in catalase activity in the liver and heart are supported by increases in antioxidant status in diabetic rats. Diabetes reduced the activity of GSSG-Red. In type II diabetes, this enzyme’s activity is reduced. Interestingly, *Z. lotus* L. leaf and root extracts, but not seed extracts, increased the activity of this enzyme in diabetic rats. The leaf and root extracts also reduced catalase activity and GSHPx, both of which were elevated in diabetic rats [161]. These effects may be due to the reduction of antioxidant, lipid peroxidation, and anticholesteroleric activity caused by the polyphenols and flavonoids of Jujuba plant extracts [162]. The saponification effect on the molecules from the temperature and sonication time on one another proved that the extraction yield for polar molecules in a hydro-alcoholic solvent is increased by extended sonication times [158].

5.3. Chia seeds

Similarly, unsaturated fatty acids positively affect health conditions such as coronary heart disease, cholesterol levels, and cardiovascular health [163]. USAE was used to extract oil from chia seeds which showed a higher yield than other extraction methods (p < 0.05). A relative 27.24 % oil yield was obtained at a temperature of 50 °C and solvent to seed ratio of 12 ml/g for 40 min. Sonication enables bubbles to form in the cavitation zone and either stay stable, causing just micro stirring, or they can increase and collapse, creating high temperatures and pressures that cause turbulence and shear waves. Positively promoting the sonophysical effect and raising the analytes’ solubility makes it easier for the extractor solvent to diffuse into the matrix. More unsaturated fatty acids are in the sonicated sample and thus beneficial for cardiovascular health [164]. Likewise, Anna Abdulshahi et al. [165], studied the effects of choosing different extraction techniques that affect the make-up of fatty acids in the oil. A clinical study on Wistar rats fed with chia seed oil in sucrose-rich diets found that the condition of cardioprotectivity and glucose oxidation is improved or reversed with normalization of blood pressure against the impaired myocardial lipid utilization observed in the control group fed with corn oil. Thus, chia seed oil could be used as an alternate strategy for managing metabolic changes related to cardiovascular health [166]. Increased intra-myocellular fat levels, fatty acid metabolites, and disturbance of the delicate balance of glucose in the heart have a crucial impact. Insulin resistance, cardiac lipotoxicity, and heart failure are all factors to consider [166]. Chia seed lowered plasma Thyroglobulin (Tg) levels by decreasing hepatic very low-density lipoprotein (VLDL)-Tg secretion while boosting plasma Tg clearance. Because of chia seed’s hypotriglyceridemic action and decrease in fatty acid translocase cyclodextrin (FAT/CD) 3 plasma membrane levels, lipid availability for Tg production in white adipose tissue (AT) may be diminished, increasing fat storage [167].

Obesity, especially abdominal (visceral) obesity, is linked to several cardiometabolic risk factors, including insulin resistance (IR), glucose intolerance, dyslipidemia, and hypertension, all of which are part of the Metabolic Syndrome (MS). Thus, in a similar study, when rats were fed with chia seeds in a sucrose-rich diet (SRD), it was found that chia seeds lowered the abdomen and thoracic circumferences, carcass fat content, adipose tissue weights, and visceral adiposity index. A boost followed this in insulin sensitivity and a better lipid profile in the blood. The decreased fat cell triglyceride content was linked to lower FAT/CD 36 plasma membrane levels and fat production enzyme activity in epididymal adipose tissue. Thus, chia seed supplementation can influence essential lipid metabolic pathways in adipose tissue, resulting in less visceral fat accumulation in SRD-fed rats [167].

5.4. Propolis

Using ultrasounds to extract different bioactive compounds from food waste increases its yield compared to the conventional extraction methods with good bioactivity, which helps enhance health [168]. Propolis is a resin produced by the bees consisting of beeswax and nectar from different flowers. In a study, the Propolis from four areas in Tunisia (a North African Country) were investigated for their bioactive compounds extracted using ultrasound and conventional methods. The study determined angiotensin-converting enzyme inhibition, which resulted in higher than 90 % extraction content of different compounds such as adpic acid, gallic acid, caffeic acid, ferulic acid, etc., which was predominantly higher (mg/g of propolis) in the ultrasonic assisted method when compared to that of the conventional solvent extraction method, and this is due to the strong disturbance of sonolysis effect on the sonication that causes the cell wall to disrupt and enhance the release of a higher number of bioactive compounds [169]. The Adpic acid 0.380 ± 0.078 mg/g [170], Gallic acid 0.082 ± 0.035 mg/g [171]. Caffeic acid 0.353 ± 0.044 mg/g [172]. Gallic acid function in *E. Officinalis* mediated anti-diabetic potential and characterized the increase of pAkt, PPAR-γ, and Glut 4 in gallic acid mediated anti-diabetic activity, offering prospective treatment for diabetes and related disorders. Gallic acid increases insulin sensitivity by activating protein kinase (Akt) rather than adenosine mono phosphate (AMP); it activates adenosine mono phosphate activated protein kinase (AMPK), and insulin sensitivity is mediated by both Akt and AMPK activation [171].

Studies proved that Ultrasound assisted extract has higher amounts of total phenolic content (2200–3300 mg GA/100 g), ACE inhibition activity (97–100 %), and Antioxidant activity (140–250 µmol Trolox/100 g) when compared to the conventional reactor extraction which
resulted in total phenolic content (1800–2200 mg GA/100 g), ACE inhibition activity (94–99 %), antioxidant activity (110–150 μmol Trolox/100 g) [169].

The effects of Propolis Ethanol Extract (PEE) between 200 and 600 mg/kg on blood sugar, lipid metabolism, and the protein level of poly-(ADP)-ribose polymerase (PARPs) in streptozotocin-induced diabetes male Wistar rats were examined in this study. The principal bioactive substances detected in South-western Nigeria Propolis include α - and β - amyrin, mono- and polysaturated fatty acids, phenolic compounds, taxaraxetol, and lupeol. The compounds exhibited the following changes, including reduction of hyperglycaemia, hyperlipidaemia, lipotoxicity, weight loss, and attenuation of hepatic PARPs levels, implying that it could be a source of conveniently available, affordable, and effective treatment for diabetes and its comorbidities [173]. The decrease in blood glucose levels could be due to some bioactive constituents of encapsulated propolis having a protective effect on pancreatic β cells or increased peripheral utilization of glucose by direct stimulation of glucose uptake and inhibition of glucose transporter activity from the intestine, or bioactive elements with hypoglycaemic properties, such as phenolic acids, which increased insulin secretion in vivo [174].

5.5. Sweet granadilla

Passiflora ligularis is a climbing shrub mainly found in Mexico, northwest and South America. It is known for its edible fruit. The optimization of flavonoid content from P. ligularis leaves using USAE was studied. The cavitation effect increases the penetration of the solvent into the medium and the release of desired compound [178]. The effect of high flavonoid content on the extract activity was investigated for in vitro antilglycation assay and in vivo glucose tolerance test in mice. The optimized conditions were 63 % ethanol at 70 °C for 33 min of USAE. The predicted highest flavonoid yield (i.e., 57.77 mg-isoquercetin equivalent/g dry extract) and the experimental high flavonoid content (59.76 ± 1.90 mg equivalent/g dry extract) are correlated and are highly consistent. This increasing in the yield is due to increase in the number of hydroxyl group of the molecule, creating new flavonoids, which is represented in Fig. 2. After 30 mins of exposure of the mice to the crude extract and the optimized ultrasound-assisted extract (500 μg/ml), studies showed that the blood glucose levels were elevated in that of crude extract. 56.77 ± 0.78 % inhibition of AGE formation is observed for the flavonoid extract of 54.68 ± 1.13 mg Q/g DW at the conditions (50 °C and 60 % ethanol for 20 mins). This proves that the optimized ultrasound-assisted extract has higher hypoglycaemic activity, i.e., anti-diabetic activity [175].

Studies, where percolation was selected as the extraction method for isolating the total flavonoid content in Passiflora ligularis species were conducted by Sandra M et al. [176]. The ethanol concentrations of 25 %, 50 %, and 75 % under the extraction times of 24, 48, and 72 h, where the maximum yield of the total flavonoid content was observed to be 55.12 ± 0.63 mg- eq vitexin/g DW [176]. In a study by Ray et al., the aqueous and ethanol extracts of Passiflora ligularis juss are studied for anti-diabetic activity in hyperglycaemic male Wistar rats. The aqueous extract and its ethanol fraction from P. ligularia leaves (125 mg/kg to 500 mg/kg) lowered glycemia and raised hepatic and muscle glycogen levels in a glucose tolerance test. Isoquercetin, a flavonoid in the extract, stimulates glucose uptake without activating insulin receptors, although it involves the PI3K, MAPK, MEK/ERK pathways, and de novo protein synthesis in GLUT-4 translocation. Hence such flavonoid-rich extracts can be used as alternative natural, non-invasive medicine to alleviate diabetes [177]. Astragalus increased insulin secretion while decreasing blood sugar levels. Astragalus increased calcium influx in isolated pancreatic cells via a mechanism involving adenosine triphosphate (ATP)-dependent potassium channels, i-type voltage-dependent calcium channels, sarcolysm/endoplasmic reticulum calcium ATPase (SERCA), protein kinase C (PKC), and protein kinase A (PKA).

Astragalin, a dietary co-adjuvant, has been proven to be an insulin inducer with the potential to improve glucose tolerance [177]. In a study on Passiflora ligularis juss, H NMR signals related to polyphenolic compounds are linked with higher inhibitory activities of glucosyl-hydrolase inhibitors, mainly quercetin-3- O-β-glucoside, kaempferol-3-O-β-glucoside. Thus, these flavonoids can be utilized for treating diabetes [178].

5.6. Baobab

Adansonia digitata is a famous tree in the African continent for its nutritional and traditional medicinal qualities. The bioactive compound extraction methods from Adansonia digitata fruit pulp were compared using high-intensity ultrasound and thermal treatments. These bioactive compound extraction methods using the high-intensity ultrasound (at intensities of 687 W/cm² for 5 mins and 344 W/cm² for 15 mins, (p < 0.05)) has more benefits compared to the thermal treatments, such as more phenolic content (814.29 ± 28.31 mg GAE/100 g DW) flavonoid content (3897.63 ± 4.56 mg RE/100 g DW), antioxidant activity and a high inhibitory activity of α-amylase (95 % inhibition at 0.5 mg/ml sample concentration.) and α-glucosidase (90 % inhibition at 0.5 mg/ml sample concentration) [179]. The anti-glycation activity of Adansonia digitata extract was previously reported [180]. α- amylase and α- glucosidase inhibitory activity while subjected to ultrasound and thermal treatments were compared with the acarbose (control) at the same concentration of 0.1 to 0.5 mg ml⁻¹ [160]. The results showed that the samples treated with ultrasound had higher α-amylase and α-glucosidase inhibitory activity. The total phenolic content (814.29 ± 28.31 mg GAE/100 g DW) and total flavonoid content (3897.63 ± 4.56 mg RE/100 g DW) were higher in the ultrasound treated samples. This is due to the high-intensity cavitation of the sonochemical effect, which results in the higher availability and the alteration of the primary structure of the phenolic and flavonoid compounds, ultimately proving the higher number of compounds in the extract [181]. This is due to the high-intensity cavitation effect, which results in the higher availability and the alteration of the primary structure into phenolic and flavonoid compounds, ultimately proving the higher number of compounds in the extract [181]. Several studies state that the Adansonia digitata is a significant source of proanthocyanidins and has more content when compared to blueberries, strawberries, apples, etc., [182]. Bioactive compounds from different sources and their bioactivities are listed in Table 4.

Hussain et al [183] investigated the effect of extraction techniques like Maceration to isolate polyphenols and flavonoids from Adansonia digitata. The yield was total phenolic content of 272 ± 1.2 mg GAE/g with 50 % ethanol concentration and total flavonoid content of 26 ± 2 mg QE/g with 50 % ethanol extract [183]. An antidiabetic study on human subjects with water-based extract of whole fruit of Adansonia digitata (baobab) was reported by Rita et al., and others found that the intervention group’s Glycemia incremental area under the curve and glucose maximal concentration was significantly lower than the control group. By boosting the level of GLP1, epicatechin and procyanidins B2 and C1 in the extract enhance insulin production, which helps to improve blood glucose response. GLP-1 secretion has been observed to increase following ingestion of certain polyphenol extracts via a cAMP-dependent route. Polyphenols also prevent glucose from being transported from the intestinal lumen to the cells through the glucose transporters SGLT1 and GLUT2. This study also discovered that polyphenols in baobab extract had a potent antioxidant and reactive oxygen species inhibitory capacity. Procyanidins B2 can also help with oxidative stress by inhibiting the production of advanced glycation end products in pancreatic cells, which is caused by reactive oxygen species during hyperglycaemia. Peroxidation and pro-oxidation reactions produce oxidative stress in hyperglycaemic scenarios. The formation of reactive oxygen species (ROS) and cellular mitochondrial dysfunction happens due to the advanced glycation of proteins and lipids. As a result, these antioxidants help to prevent endothelial dysfunction [184]. anti-
diabetic action includes Chlorogenic and ferulic acids; both stimulate transporters and have anti-diabetic properties. They demonstrated significant effectiveness in inhibiting two necessary enzymes (ɑ-amylase and ɑ-glucosidase) involved in converting dietary carbohydrates into glucose in their investigation. These phenolics are antioxidants and can work against diabetes by influencing insulin receptors’ function. They increase glucose transporter isoform 2 (GLUT)2 expression in pancreatic islets and improve, notably with the BuOH fraction, which had anti-inflammatory characteristics and relieved streptozotocin-induced pancreatic damage [184].

A similar study by Mohammed et al. has also indicated the antidiabetic activity of 3 different extracts of fruit pulp of baobab of 200 mg/kg in diabetic rats, viz., butanol, petroleum ether, and ethyl acetate extracts. The findings showed that diseased rats showed promising results with carbohydrate and fat metabolism and antioxidant activity, including clear protection of pancreatic sections isolated from extract-fed animals [185].

6. Conclusion and future prospects

The term “Food as medicine” has become a trend worldwide. The demand for functional food with bioactives is increasing in the consumer market. These bioactives are nothing but the engineered biomaterials obtained using the process of ultrasonication. The demand for non-thermal processing technology in food processing, preservation, and nutrition has given birth to ultrasonic processing, a novel technology. The nature of such a revolutionary technique is the basis for its encouragement. It preserves the organoleptic features like flavor, color, taste, appearance, and textural properties of bioactive while reducing the need for preservatives and chemicals during extraction. Consumer demand for high-quality food with antioxidant, anticancer, antimicrobial, anticholesterol, and bioactives with good efficacy has a wide range of applications in fields such as pharmaceuticals, medicine, functional food, etc., to provide non-invasive medical treatments. The most fantastic aspect of this advanced approach is its practicality and efficiency in employing the principle of acoustic cavitation. The challenges before ultrasonic processing are to lower the cost, increase the amplitude power of ultrasonic equipment, and make it more cost-effective for food, etc., to provide non-invasive medical treatments. The most non-thermal processing technology has enormous scope for innovation and has created numerous non-thermal processing research and development opportunities. For the reasons stated, as well as recent discoveries and studies in the field, it will result in significant changes in the production of non-invasive biomaterials.

Ultrasonic Assisted Extraction is a non-conventional extraction technique whose main advantage over the other extraction techniques is that it uses no thermal treatment, lower solvent usage, and lesser time consumption. To conclude, several bioactive compounds from different natural sources can be extracted using ultrasound with high efficacy and various biomedical properties. These ultrasound extracted products are rich in enhancing cardiovascular health, anti-diabetic properties, anti-obesity properties, antioxidant properties, anti-cancer properties, anti-
microbial properties, etc. Several studies focused on the properties mentioned earlier of the ultrasound extracted compounds and concluded that this extraction method is significant in increasing the yield and biomedical properties.

Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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