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A comprehensive review on anthocyanin-rich foods: Insights into extraction, medicinal potential, and sustainable applications

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ABSTRACT

Anthocyanins (ACNs) are natural pigments commonly found in plants which contribute to the vibrant colors of fruits, vegetables, and flowers. The present review aims to cover the ACNs field in terms of sources, extraction/purification techniques, as well as characterization methods that are crucial for assessing their medicinal potential and sustainable applications. Characterization methods e.g. HPLC, UPLC-QTOF-MS, MS, and NMR are discussed as analytical tools for the identification and quantification of ACNs in various vegetable matrices. Their antioxidant, anti-inflammatory, antidiabetic, anti-cancer and cardiovascular properties are, also, highlighted. Besides, the use of ACNs as natural colorants, preservatives, and functional ingredients is discussed considering their impact on the food industry. Likewise, due to their anti-aging and skin-protective properties, their employment in the cosmetic field is reported making them appealing for skincare formulations. This review provides a comprehensive overview, emphasizing the ACNs versatility in medicine, food industry, and cosmetic field, fostering future research and innovation.

1. Introduction

In contemporary times, food is acknowledged as a crucial supplier of dietary substances and biologically active compounds, contributing to the enhancement of human health and overall well-being. The growing awareness among consumers regarding the profound impact of diet on health is evident in their preference for natural products rich in vitamins, minerals, and various bioactive compounds e.g. carotenoids, peptides or anthocyanins (ACNs) [1]. ACNs are a group of bioactive pigments naturally found in common plants. From a chemical view-point, ACNs belong to the flavonoids group, a subclass of the polyphenol family, contributing to the attractive orange, red, purple, violet, and blue colors of fruits, vegetables, and flowers [2]. Berries, currants, grapes, and some tropical fruits are reported to possess a high ACNs content [3]. There are many different ACNs in nature and the six most common are represented by cyanidin, delphinidin, malvidin, peonidin, petunidin and pelargonidin [4]. ACNs occurring in berries, blackcurrants, and other types of red to blue-colored fruits, vegetables and flowers have been reported to be strong antioxidants. Moreover, anthocyanin-rich foods e.g. black carrots, red cabbages, and purple potatoes are potential functional foods [3].

ACNs are known for their sensitivity to pH, light, and temperature [5], thus facing challenges in traditional extraction methods, mainly due to time consumption which negatively affect the antioxidant activity. Modern extraction technologies, such as ultrasonic-assisted extraction (UAE), offer efficient alternatives. UAE is cost-effective, time-efficient,

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and easily scalable to an industrial level. Further, the use of UAE contributes to a reduction in extraction time, preserving integrity of ACNs compared to other extraction methods [6].

From a pharmacological viewpoint, ACNs have been widely studied for their medicinal values. ACNs are reported possess antidiabetic, anticancer, anti-inflammatory, antimicrobial, and anti-obesity effects, as well as a positive effect on cardiovascular diseases (CVDs), making them potential pharmaceutical ingredients [3].

Fruits stand out as the predominant dietary reservoir of ACNs, contributing up to 70 % of daily intake. Notably, apples, pears, berries, stone fruits, and grapes are major sources. In Europe, wine can also account for approximately 25 % of anthocyanin intake [7]. Berries take precedence as the primary dietary source in the US and Northern Europe [8,9]. Although ACNs are not classified as essential nutrients, China has recommended a daily intake of 50 mg [10]. Estimating daily anthocyanin intake is challenging due to incomplete data on their quantities in food. However, it is approximated to be around 12.5 mg/day in the US, ranging from 19 to 65 mg/day for men and 18–44 mg/day for women in Europe. Some studies indicate an average intake of approximately 24 mg/day in Australia, while in Finland, it could reach up to 150 mg/day, primarily sourced from berry consumption [4,7]. Given the recognized health benefits of ACNs, promoting the consumption of fresh fruits and vegetables becomes essential to ensure an ample supply of antioxidant and protective substances in the bloodstream. Regular intake of fruits and vegetables is a crucial aspect of a healthy lifestyle, offering protection against chronic and degenerative diseases [11].

The effects of brown, purple, and red rice bran extracts on the inhibition of two digestive enzymes (α-amylase and α-glucosidase) as well as their effect on the insulin-signaling transduction pathway has been investigated [12]. Alternatively, ACNs have been also studied for their potential anticarcinogenic properties. Exploration of the plausible antitumor and anticancer roles of ACNs across various stages of tumorigenesis and carcinogenesis thorough an examination of their sources, structural features, and health implications has been subject of selected studies. The focus was to understand the pharmacological aspects of ACNs in both in vitro and *in vivo* settings for cancer prevention and treatment [13].

Daily consumption of fruits and vegetables has been associated with a decreased risk of CVDs, most likely due to the abundance and variety of bioactive compounds e.g. ACNs [14,15]. As an alternative to pharmaceutical medications, the consumption of a diet rich in natural bioactive components has been reported to improve cardiovascular properties and it has been a subject of various researches [16].

ACNs, derived from medicinal plants, have been incorporated into cosmetic products through the integration of traditional herbal knowledge with advanced cosmetic technology [17]. These products are not only safe but also widely accepted. Plant materials containing ACNs offer diverse active ingredients, promoting skin soothing, active healing, and protection [18]. The skin, a vital external biological barrier, regulates body temperature, water content, and lipid stores, making it susceptible to oxidative stress. Essential in cosmetic skin creams is the inclusion of antioxidants of berries, black currents, plum, apple, grape, red cabbage and onion to prevent damage from UV rays, environmental pollution, passive smoking, and other stressors [19].

In this review, extraction, purification and characterization of anthocyanin-rich foods are discussed along with their properties as functional active ingredients and therapeutic agents for disease prevention and treatment.

2. Sources and distribution of ACNs

Berries like blueberries, strawberries, raspberries, blackberries, cranberries, cherries, and red or violet grapes are rich sources of ACNs (Fig. 1). Vegetables such as red cabbage, eggplant, and red onions, especially those with a reddish or purplish hue, also contain significant concentrations of these compounds [20]. Additionally, grains like black rice and specific types of corn, such as purple corn, contribute to the abundance of ACNs [21]. Legumes like black soybeans, along with flowers like hibiscus and roses, are notable for their discernible ACN content. Herbal and spice components like blackcurrant, bilberry, and black elderberry are recognized for their elevated ACN levels (Fig. 1) [22]. These ACNs are known for their health-enhancing properties, including antioxidant and anti-inflammatory effects. Table 1 emphasizes that cyanidin-3-glucoside (C3G) is a prevalent ACN naturally occurring in black rice, black beans, purple potatoes, and various colorful berries. C3G, with its strong antioxidant activity possibly attributed to the two hydroxyls on the B ring, is abundant, as is cyanidin 3-galactoside in various fruits and vegetables [23]. A pharmacokinetic study in humans identified over 20 types of C3G in serum [24]. Sweet cherries, as studied by Kent et al. [25], showcase a concentration of 143.3 mg/100 g of

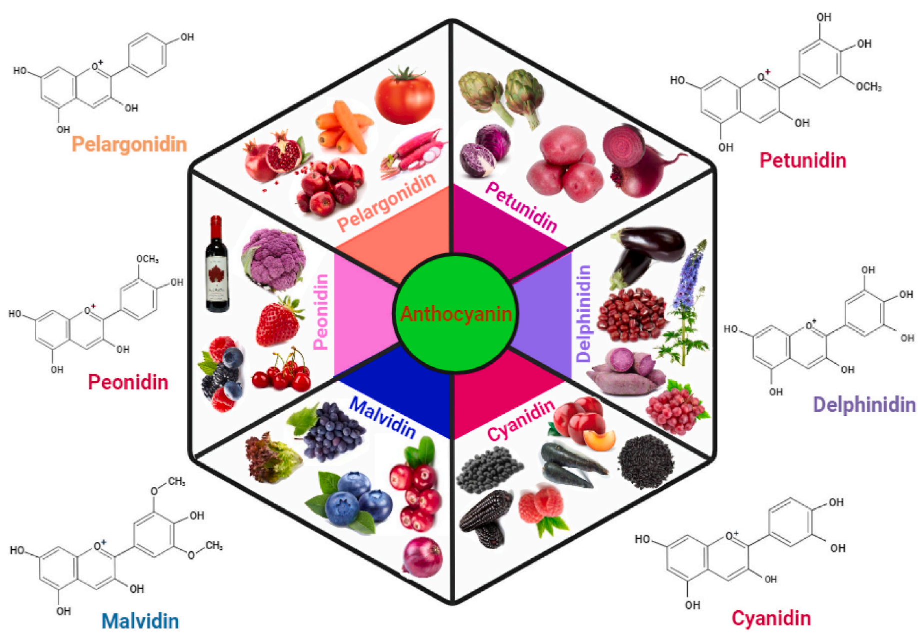

Fig. 1. Sources and chemical structure of ACNs (Source from ww.biorender.com).

Table 1
The constitution of ACNs found in diverse fruits, vegetables, legumes, and grains.

Fruits/vegetable legumes/grains	Types	Major ACNs	ACNs content (mg/100 g)	References
Berries	Blackberries	Cyanidin-3-glucoside	138.72	[37]
	Blueberries	Malvidin-3-glucoside	85–270	[38]
	Chokeberries	Pelargonidin-3-glucoside	47.2	[39]
	Elderberries	Cyanidin-3-glucoside	794.1	[40]
	Strawberry	Pelargonidin-3-glucoside	335.08	[41]
	Crowberry	Cyanidin-3-galactoside	0.804	[42]
		Delphinidin-3-galactoside	0.862	
Cherries	Sweet cherries	Cyanidin-3-O-rutinoside	143.3	[25]
	Black cherries	Cyanidin-3-O-glucoside	43.6	[25]
	Sour cherries	Cyanidin-3-O-glucosyl-rutinoside	3–44	[43]
Plums	Jojo plums	Cyanidin-3-galactoside	5.6	[44]
	Valor plums	Cyanidin-3-glucoside	23.4	[45]
	Cacanska rodna	Cyanidin-3-rutinoside	7.4	[45]
	Cacanska najbolja	Peonidin-3-rutinoside	36.6	[45]
Pomegranates	*Punica granatum*	Delphidin-3,5-diglucoside	54.5	[27]
		Cyanidin-3,5-diglucoside	104.3	
		Pelargonidin-3,5-diglucoside	9.8	
		Delphidin-3-glucoside	35.5	
		Cyanidin-3-glucoside	155.3	
Apple	Red Apple	Cyanidin-3-glucoside	36.1	[46]
Vegetables	Black carrots	Cyanidin-3-galactoside	18.85	[30]
	Red onion	Cyanidin-3-(6″-malonylglucoside)	1.6	[31]
	Red cabbage	Cyanidin-3,5-diglucoside	31.0	[20]
	Red lettuce	Cyanidin-3-(6″-malonylglucoside	200	[29]
	Red oak leaf	Cyanidin-3-(6″-malonylglucoside)	400	[29]
	Purple corn	Cyanidin-3-glucoside	290	[47]
Legume-	Black soybean	Cyanidin-3-glucoside	0.94–15.98	[33]
		Delphinidin-3-glucoside	0–3.71	
		Petunidin-3-glucoside	0–1.41	
	Red kidney bean	Cyanidin-3-glucoside	47	[48]
	Peanut	Cyanidin-3-glucoside	13.85–23.31	[34]
	Lentils	Delphinidin-3-glucoside	0.66	[35]
	Black Rice	Cyanidin-3-glucoside	0.057	[36]
		Peonidin-3-glucoside	29.78	
Flowers	Red rose	Cyanidin-3-O-glucoside	0.61–502.64	[49]
	Hibiscus	Cyanidin-3-glucoside	395.3	[50]
	Red campion Petunia	Delphinidin-3-O-sambubioside	361.99	[51]

cyanidin-3-O-rutinoside and cyanidin-3-O-glucoside. Quercetin-3-O-rutinose is also substantially present in sweet cherries (Table 1). The variation in anthocyanin (ACN) content across different berry types, which contain glycosides of cyanidin, can be attributed to the inherent acidity of these fruits. The acidic environment affects the stability and composition of ACNs, leading to diverse profiles among berries. Interestingly, malvidin, peonidin, and petunidin are less commonly found in berries compared to cyanidin-derived glycosides, potentially due to their susceptibility to degradation or limited biosynthesis pathways within these fruit varieties. This variation underscores the complex interplay of environmental factors, genetic predispositions, and metabolic processes shaping the composition of ACNs in berries [3]. Mulberry fruit's principal ACN is C3G, followed by cyanidin-3-rutinoside (C3R). High-speed counter-current chromatography identified five ACNs in mulberry fruit, including C3RG, C3RGa, C3G, C3Ga, and C7G [26]. Pomegranates (*Punica granatum*) are renowned for their abundant ACN content, with delphinidin-3,5-diglucoside, cyanidin-3,5-diglucoside, and pelargonidin-3,5-diglucoside contributing to their antioxidant properties [27].

Vegetable sources like radish, purple sweet potato, or red cabbage provide a higher percentage of acylated ACNs than fruits. Black carrots, within their diverse spectrum, contain cyanidin 3-xylosylgalactoside, cyanidin 3-xylosyl, and other unique flavonoid compounds [28]. The crimson cohort, including red onion, red lettuce, and red oak leaf, features cyanidin-3-(6″-malonylglucoside), a structurally intricate ACN derivative with malonylglucoside moieties [29–31]. Red cabbage reveals cyanidin-3,5-diglucoside, characterized by the presence of tandem glucoside units [20]. In black soybeans, Cyanidin-3-glucoside is the major compound, followed by delphinidin-3-glucoside and petunidin-3-glucoside [32]. Red kidney beans exhibit a substantial content of cyanidin-3-glucoside, while peanuts display variable amounts of this compound. Lentils contain approximately 0.66 mg of delphinidin-3-glucoside, and in black rice, cyanidin-3-glucoside is relatively low, but peonidin-3-glucoside is notably higher (Table 1) [33–36].

3. Extraction and purification of ACNs

ACNs undergo diverse extraction and purification methodologies in order to obtain highest yield and purity (Fig. 2). can be extracted by using diverse methods. Solid-liquid extraction (SLE) is a method to extract compounds from solid substances using solvents like ethanol, methanol, acetic acid, or formic acid. It exploits the differences in solubility among components in the solid material by breaking it into smaller particles to facilitate dissolution. After dissolution, the components are separated according to their solubility, allowing for the isolation and purification of desired compounds or fractions [52]. UAE enhances the efficiency of ACNs extraction by employing sound waves to disrupt cell structures, facilitating the use of solvents like water, ethanol, or methanol [53,54]. Solid-phase extraction (SPE) utilizes a solid-phase sorbent tailored to ACN isolation [55]. Pressurized liquid extraction (PLE), also called accelerated solvent extraction (ASE), uses elevated temperatures and pressures, always below the respective critical points, to maintain the solvent in a liquid state throughout the extraction procedure [56]. Subcritical water extraction (SWE) and supercritical fluid extraction (SFE) utilize water at elevated temperatures/pressures and supercritical CO_2, respectively, offering environmentally friendly alternatives [57].

Various solvent systems, including ethanol, methanol, trifluoroacetic acid, acetone, ethyl alcohol, citric acid, acetic acid, and hexane, are

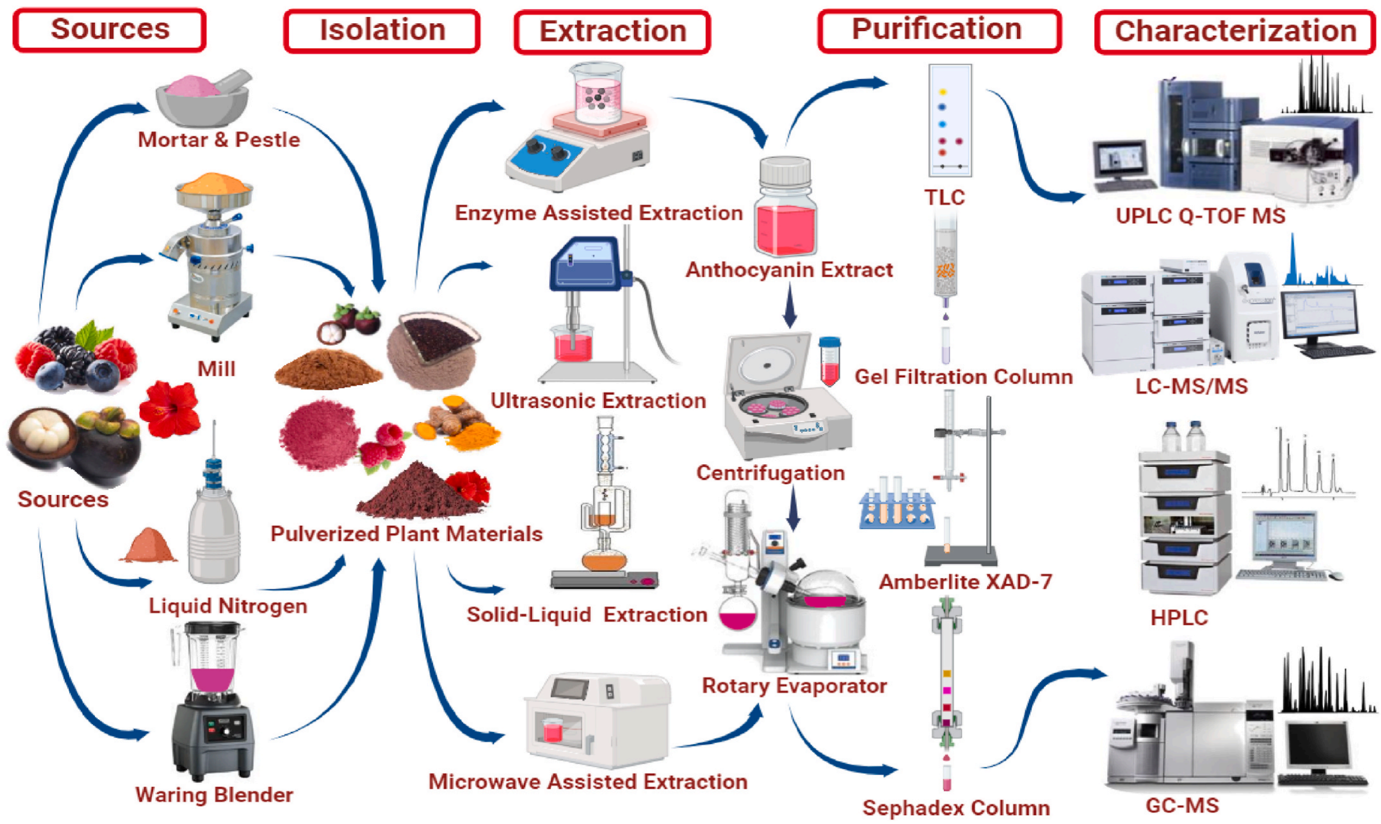

Fig. 2. Schematic representation for the extraction, purification and characterization of ACNs (Source from www.biorender.com).

employed in different ratios for ACN extraction. Alternatively, mineral acids like hydrochloric acid (HCl) and sulfuric acid adjust pH and aid in extraction (Table 2). These methods enable efficient isolation of ACNs from diverse natural sources [58].

ACNs are generally extracted from plant, food and agricultural samples using ethanol/methanol water mixtures acidified with HCl, formic acid, or other organic acids like citric acid. For specific purposes, 70 % aqueous acetone is another commonly used solvent. Stronger and more lipophilic organic solvents with ultra-sonication and temperature aid are chosen for matrices resistant to acidic homogenization, such as plant seeds. Liquid matrices like red wine, pomace, and juices are treated with alcoholic acidic solutions [59].

While effective in extracting various compounds, solvent extraction requires large amounts of solvents and raises environmental concerns due to solvent disposal. Acid extraction, on the other hand, relies on acidic conditions to release ACNs from the plant material, resulting in higher yields compared to solvent extraction and being more environmentally friendly. However, it requires precise pH control and might degrade sensitive compounds [60,61]. Enzyme-assisted extraction involves the use of enzymes such as cellulase or pectinase to disrupt cell walls and release ACNs. Although gentle and specific, this method can be time-consuming and costly due to enzyme used. The choice of extraction method depends on factors like efficacy, environmental impact, and the characteristics of the ACNs being targeted [62,63].

SLE stands out for its simplicity and scalability, requiring minimal equipment. UAE provides rapid extraction with reduced solvent and energy consumption, although its efficiency depends on factors like ultrasonic power and frequency. PLE offers higher efficiency and shorter extraction times due to pressure and heat application. SFE utilizes environmentally friendly supercritical fluids but demands specialized equipment.

For ACN extraction from cranberries, various methods have been employed e.g. solvent extraction with acidified methanol or ethanol, enzyme-assisted extraction, PLE, and SFE. Each method offers advantages in yield and quality. Other studies indicate that both ultrasound and microwave-assisted methods can enhance cranberry extraction yields [61], followed by purification employing Sephadex LH-20, a size exclusion chromatography resin renowned for its molecular size discrimination capabilities [52]. For blackberries, blueberries, chokeberries, and strawberries diverse methods have been employed. Solvent extraction with acidified methanol, ethyl acetate or ethanol, enzyme-assisted extraction, PLE, and SFE are the most utilized. UAE can yield more than the other extraction methods (108.23 mg/100 g); their subsequent purification converges on the application of resin-based methodologies, with AB-8 macroporous resins demonstrating adeptness in purifying ACN extracts [53,64,65]. A commonality emerges in the use of Amberlite XAD-7 and its high-performance variant, 7HP resin, serving as pivotal purification agents for blackcurrant, red cabbage, onion, black peanut, and pomegranate ACNs, emphasizing the versatility of resin-based purification across botanical sources [55,57,66–68].

Furthermore, UAE is harnessed for purple corn and deep eutectic solvent (UADESE) for black carrot, accentuating the diversity in extraction methodologies [69]. Grape ACNs, extracted through SLE with acidified aqueous methanol and aqueous ethanol, undergo purification utilizing diaion HP-20 macroporous resin, showcasing the adaptability of resin-based purification across solvent systems [70]. The nuanced extraction of purple sweet potato ACNs involves purging with nitrogen gas, while black beans, subjected to SFE with a CO_2-ethanol mixture, accentuates the emerging trends in sustainable extraction practices (Table 2) [71].

4. Characterization of ACNs

The chemical characterization of ACNs within a myriad of botanical sources unveils a diverse array of analytical methodologies. High-performance liquid chromatography (HPLC), coupled with

Table 2
Extraction, purification and characterization of ACNs derived from different diverse fruits, vegetables, legumes, and grains.

Types	Extraction	Purification	Characterization	Compounds	References
Cranberry	Acetone: water: acetic acid (70:29.5:0.5; v/v/v) (SLE)	Sephadex LH-20	HPLC, HPLC-ESI-MS	Procyanidin	[52]
Blackberries	HCl (0.25 %): ethanol (80 %), solid-liquid ratios of 1:15 for 12 h at 40 °C (SLE)	AB-8 macroporous resins	UPLC-QTOF-MS	Cyanidin-3-O-glucoside	[64]
Blueberries	HCl (0.3 %) with ethyl alcohol (95 %) at 40 °C for 30 min (UAE)	AB-8 macroporous resins	HPLC-ESI-MS/MS	Cyanidin 3-O-glucoside	[53,54]
Chokeberries	Water with citric acid (1 %) (SWE)	Amberlite XAD7 column	HPLC-MS, SEM	Malvidin-3-galactoside, cyanidin-3-galactoside	[56,72]
Strawberry	HCl (0.2 %) in MeOH (SLE)	Inertsil ODS-3 C18 (150 × 4.0 mm, 3 μm)	RPLC-DAD	Cyanidin-3-glucoside, pelargonidin-3-glucoside	[65] [83]
Sour cherry	The freeze dried hydroalcoholic extracts (SPE)	DSC-18 SPE Tube column	HPLC-DAD, MS/MS	Cyanidin-3-sophoroside, cyanidin-3-glucoside, cyanidin-3-rutinoside	[75]
Sweet cherry	20 mL of ethanol: water (70:30) (SLE)	Sep-Pak C18 column	HPLC-DAD-ESI/MS, HPLC-DAD.	Delphinidin 3-O-rutinoside, cyanidin-3-O-rutinoside	[76]
Black current	Acidified water (600 mL) with HCl (0.01 %; v/v) (SPE)	Amberlite XAD-7HP resin	HPLC, mass spectrometry, IR, NMR, and UV–Visible spectroscopy, ^{1}H and^{13}C NMR, HPLC, HR-MS, AR FT-IR	Delphinidin-3-O-rutinoside, cyanidin-3-O-rutinoside	[55]
Plum	HCl (0.15 %) in acetone for 4 h in the dark at 4 °C. (SLE)	C-18 Sep-Pack cartridge	HPLC	Cyanidin 3-glucoside, cyanidin 3-rutinoside	[77]
Apple	Acetone: water (7:3; v/v), methanol: water (1:1; v/v) (SLE)	Sephadex LH-20 column	FTIR, ^{1}H and^{13}C NMR, ESI and MALDI-TOF MS	Proanthocyanidins	[74]
Grape	Acidified aqueous methanol and aqueous ethanol (0.01 % HCl) at varying alcohol-to-water ratios. (SLE)	Diaion HP-20 macroporous resin	UV-VIS DAD, Q/TOF MS, ESI and HPLC-DAD-MS	Cyanidin-3-glucoside	[58,70]
Pomegranate	Methanol: water (50:50; v/v; pH 2.0) with acetone: water (70:30; v/v) (SLE)	Nova-Pak C18 column (250 × 4.6 mm, 4 μm)	HPLC−ESI−QTOF, MALDI-TOF	Proanthocyanidins	[68,84, 85]
Red cabbage	Mixture of water, HCl, methanol, and acetone (SLE)	Amberlite XAD-7HP	HPLC	Cyanidin-3-glycoside	[66]
Black carrot	Water (UAE) deep eutectic solvent (UADESE)	Amberlite XAD-7	HPLC-ESI-MS	Pyranoanthocyanin	[69]
Purple corn	The ultrasonic power were 400 W and 90 times (UAE)	AB-8 macroporous resin	HPLC-DAD-ESI-MS/MS	Cyanidin-3-O-glucoside	[86]
Onion	Acidified methanolic extracts (SLE)	Amberlite XAD-7	UV–Vis spectrum, HPLC-DAD, HPLC-ESI-MS, 2D NMR spectroscopy and LC–MS.	3-O-β-glucopyranoside, 3-O-(6″-O-malonyl-β-glucopyranoside) of 5-carboxypyranocyanidin	[67]
Purple sweet potato	7 % acetic acid in 80 % methanol was purged with nitrogen gas (SLE)	Amberlite XAD-7HP	HPLC-DAD and LC/MS/MS analysis	Cyanidin and peonidin	[78]
Black beans	composed of 90 % CO_2 gas and 10 % acidified ethanol/water 50/50 v/v (0.3 % formic acid) (SFE)	Amberlite XAD-7HP	HPLC, DART-MS spectrometry	ACNs	[71]
Black rice bran	Ethanol: water mixture (60:40 water (SEM)	Amberlite XAD-7HP	HPLC-ESI-MS/MS	Delphinidin-3-glucoside and cyanidin-3-glucoside	[79]
Red rice	Extracted twice with hexane (1:8 bran to solvent ratio), followed by extraction twice with 70 % ethanol for 2 h (SLE)	Sephadex LH-20	HPLC- LC-MS	Cyanidin 3-glucoside	[10,80]
Black peanut	Deionized water acidified with HCl (pH 2.0) at 70 °C for 10 min (SLE)	Amberlite XAD-7HP resin	HPLC-PDA-ESI–MS/MS and ^{1}H,^{13}C NMR spectroscopy	Cyanidin-3-O-sophoroside, cyanidin-3-O-sambubioside	[57]
Hibiscus	Acidified methanol with trifluoroacetic acid (0.1 %; v/v) for 24 h at 4 °C (SLE)	gel XAD-7,	Centrifugal Partition Chromatography, HPLC	Delphinidin 3-O-glucoside	[81]
Rose	20 mL 80 % methanol (SLE)	C18- HPLC column	HPLC-PAD	Cyanidin 3,5-diO-glucoside, pelargonidin 3,5-di-O-glucoside	[82]

electrospray ionization mass spectrometry (ESI-MS), is a prominent methodology employed for the identification of procyanidins, providing a detailed insight into the composition of these polymeric flavonoids [52]. The utilization of ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS) and nuclear magnetic resonance (NMR) analyses proves invaluable in discerning the presence of cyanidin-3-O-glucoside and malvidin-3-glucoside, elucidating the glycosidic moiety's positioning within the molecular structure, respectively [72,73]. Tandem mass spectrometry stands as a robust technique for dissecting the intricate structures of ACNs [56] as exemplified in the identification of cyanidin 3-O-glucoside and pelargonidin 3-O-glucoside [54]. This approach not only facilitates the differentiation of structural isomers but also unravels the glycosylation patterns integral to these compounds.

Furthermore, comprehensive methodologies such as Fourier transform infrared spectroscopy (FT-IR), NMR, and ultraviolet–visible spectroscopy (UV–Vis) converge to provide a holistic understanding of ACN composition [74]. High-resolution mass spectrometry (HRMS) and attenuated total reflectance Fourier transform infrared (AR FT-IR) collectively contribute to the structural elucidation of delphinidin-3-O-rutinoside and cyanidin-3-O-rutinoside, underscoring the robustness of multifaceted analytical approaches (Fig. 2) [55].

In a collective analysis of various botanical matrices encompassing blackberries, chokeberries, sour cherries, sweet cherries, black currants, plums, apples [74–77], grapes, pomegranates, red cabbage, black carrots, purple corn, onions, purple sweet potatoes, black beans, black rice bran, red rice and black peanuts [57,71,78–80], hibiscus and roses, these methodologies consistently delineate the presence of ACNs such as cyanidin-3-glycoside, delphinidin-3-glucoside, cyanidin-3-O-glucoside, and proanthocyanidins. This nuanced chemical fingerprinting establishes a venue for understanding the phytochemical diversity across a spectrum of plant sources, crucial for both analytical and nutritional perspectives [81,82].

5. Medicinal potential and sustainable applications of ACNs

5.1. Protection from urinary tract infections

Urinary tract infections (UTIs) are a common medical concern requiring outpatient care, with persistent and recurring cases leading to over one million hospital admissions annually in the USA. *Escherichia coli*, a primary pathogen involved in UTIs, Cranberries, often administered in the form of cranberry juice, have a historical role in UTI prevention (Table 3). This is attributed to cyanidin-3-O-glucoside in cranberries that hinder bacterial adherence to bladder walls, potentially reducing the occurrence of UTIs [87]. Various forms of cranberry products, including juice, capsules, tablets, and concentrates, may differ in their efficacy for UTI prevention. While blueberries are recognized for their ACN richness, the potential efficacy of cyanidin-3-O-glucoside and cyanidin-3-O-rutinoside has an adjuvant for preventing or treating UTIs remains uncertain and unclear [88,89]. Limited in vitro studies have explored their impact on uropathogenic *E. coli* strains isolated from the urine of individuals diagnosed with UTIs, with only one study extending to *Pseudomonas aeruginosa* (Fig. 3).

5.2. Antioxidant activity

ACNs found in berries, blackcurrants, and various red to blue-colored fruits not only provide the natural color but also boast strong antioxidant properties. Black carrot [90], red cabbage [91], and purple potato [92], rich in ACNs, emerge as potential functional foods traditionally consumed for disease prevention. These compounds, functioning as nutraceutical antioxidants, offer a myriad of health benefits, including antimicrobial effects and the prevention of chronic diseases. The pivotal role of ACN's health and therapeutic effects primarily stems from its antioxidative activities. The glycosylated B-ring structure significantly enhances antioxidant activity, with ortho-hydroxylation and methoxylation further amplifying these effects [93]. Acylation with phenolic acid proves to be a contributor to increased antioxidant activity. Notably, diacylation significantly enhances antioxidant activity, whereas 5-glycosylation leads to a reduction. Given the importance of antioxidants in supporting human health by inhibiting free radicals that damage cells, their potential extends to alleviating conditions resulting from oxidative stress, such as cancer, infection, heart disease, and diabetes [4]. In the context of viral infections, including coronaviral infections, which are associated with oxidative stress and heightened free radical production, antioxidants become crucial. *Aronia* berries and their phenolic components have been well-demonstrated to exhibit potent antioxidant activity, highlighting their potential role in eliminating free radicals and boosting the immune system to inhibit viral infections. Recent researches have extensively validated the antioxidant capabilities of black chokeberries and their primary phenolic components to inhibit the effects on various radical types through diverse mechanisms, contributing to a range of bioactivities. Moreover, they demonstrate inhibitory effect on 15-lipoxygenase and xanthine oxidase, enzymes linked to peroxidation and prooxidation, respectively critical sources of reactive oxygen species (ROS) in vascular cells. A study on *Hibiscus rosasinensis* has revealed a robust association between the antioxidant activity and the presence of flavonoids, phenolics, and ACNs in the extracts [94]. This affirms that these components play a pivotal role in the observed antioxidant activity [95]. Notably, ACNs, constituting the black pigment in the pericaps and tegmen (skin layers) of black rice, are also distributed throughout all layers of the rice [96]. As a result, black rice represents a rich source of substances endowed with antioxidant properties serving as formidable defenders against free radicals, known culprits in the aging process, cancer development, and various diseases (Table 3) [97].

5.3. Antidiabetic activity

Various edible plant materials, including but not limited to cranberries, chokeberries, strawberries, blackcurrant, apple, red cabbage, grape, black carrot, red onions, and sweet potato have been recognized for their potential as anti-diabetic agents. This diverse array of plant sources highlights the identification of compounds with anti-diabetic properties, indicating a promising avenue for further research and potential therapeutic applications [8,155]. One notable example is the tart cherries and its bioactive compound cyanidin 3-O-β-glucoside which show a valuable promise in managing diabetes. Research suggests potential preventive effects against type 2 diabetes, exploited in a rat study where a significant 19 % reduction in fasting blood glucose and improved glucose tolerance was attained. Extended ACN treatment over a month resulted in a 50 % decrease in fasting blood glucose and a 41 % improvement in glucose tolerance. Incorporation of 40 g/day of concentrated sour cherry juice into the diet benefitted type 2 diabetic women over 6 weeks, reducing body weight, blood pressure, and hemoglobin A1c (HbA1c) levels, showing favorable effects on blood lipids in those with hyperlipidemia (Table 3). These findings underscore the therapeutic potential of tart cherries in diabetes management, offering valuable contributions to preventive and therapeutic strategies for this prevalent metabolic disorder [118].

Blueberries are rich in bioactive ACNs, particularly with a high concentration of malvidin, a compound associated with antioxidant benefits that contribute to mitigating the risk of diabetes [156]. They emerge as a promising dietary adjunct for individuals contending with diabetes, manifesting a discernible reduction in susceptibility to type 2 diabetes mellitus. Within the ACN category, prevailing constituents encompass galactosides, glucosides, and arabinosides of delphinidin, malvidin, cyanidin, petunidin, and peonidin, with malvidins and delphinidins conventionally standing out as primary contributors to the overall ACN content [157]. *Aronia* berries have demonstrated as potential in the treatment of type 1 diabetes (T1D), a condition distinct from type 2 diabetes (T2D). T1D results from an autoimmune reaction leading to the impairment of pancreatic β cells and the consequent inability to produce insulin. Unlike T2D, T1D necessitates insulin dependence and is associated with severe organ failure due to elevated blood glucose levels. In an experimental setting utilizing a streptozotocin induced T1D animal model, where six-week-old ICR healthy male mice were injected with streptozotocin (i.p., single dose, 80 mg/kg) and subsequently orally administered an ethanol extract of *Aronia* berries (10 or 100 mg/kg) for 31 days, a notable decrease in blood glucose levels was observed. Additionally, the pancreatic β cells in the mouse pancreas were protected. These findings suggest that the consumption of *Aronia* berries holds potential efficacy in safeguarding pancreatic β cells and may offer therapeutic benefits in the context of treating T1D [158].

5.4. Effects on cardiovascular diseases

Common risk factors for cardiovascular disease encompass cardiometabolic dysfunctions such as hypertension, hyperlipidemia, obesity, glucose intolerance, and diabetes, often collectively referred to as metabolic syndrome [135]. Pomegranate consumption has shown promising effects on cardiovascular health. Human studies revealed improvements after one year of pomegranate juice intake, with a significant reduction in carotid artery thickness by up to 30 % and 21 % decrease in blood pressure. ACNs from pomegranate, protecting both low and high-density lipoprotein from oxidation distinguishes it among antioxidants, mitigating atherosclerosis development and related cardiovascular events [159].

Hibiscus sabdariffa L., also known as Karkade, is widely used for

Table 3
The extracted ACNs from fruits, vegetables, and flowers have versatile applications in medicine, food, and cosmetics.

Fruits/ vegetables/ flowers	Medicinal/therapeutic uses[a]	Food supplementary[b]	Cosmetic uses[c]	References
Cranberry	Treat urinary tract infections, antioxidant and anti-inflammatory [1]. Hepato protective, cardio protective, effects on gutmicrobiota, anti-diabetis and renal functions [2]. Prevention and management of periodontitis [3]. Inhibiting proliferation, Inducing apoptosis, and Suppressing metastasis [4]	Beverages, milk and dairy products and cranberry juice drink [1]	Anti-aging preparations [1]	[98][a 1] [99][a 2] [100][a 3] [101][a 4] [102][b 1] [103][c 1]
Blackberries	Prevention and treatment of cancer, dysentery, diarrhea, whopping cough, colitis, toothache, anemia, psoriasis, sore throat, mouth ulcer, mouthwash, hemorrhoids, and minor bleeding [1]	Topping for ice cream, yogurt, and desserts, are part of fruit beverages and jams, fresh fruit[1]	The skin creams, skin repairing [1]	[104][a 1] [105][b 1] [106][c 1]
Blueberries	Anti-cancer, anti-obesity, prevent degenerative diseases, anti-inflammation, protective vision, protective liver, prevent heart diseases, anti-diabetes, improve brain, protective lung, strong bones, enhance immunity, prevent cardiovascular diseases, improve cognitive decline [1]	Fruit juice, wine, vinegar, jam, dried fruit, pulp powder, colorant and flavoring additives [1]	Sun protection factor, UV-A protection factor [1]	[107][a 1] [108][b 1] [109][c 1]
Chokeberries	Potential of anti-oxidant activity, anti-tumor activity, anti-infective activity, prevention and treatment of cardiovascular diseases, anti-diabetic activity, neuroprotective potential [1]	Variety of Juices, Preserves, extracts, fruits teas and nutritional supplements	Prevent premature skin aging and wrinkling, moisture agents, UV filters,	[95][a 1] [110][b 1] [111][c 1]
Strawberry	Prevention of inflammation, oxidative stress, cardiovascular disease, certain types of cancers, type 2 diabetes and obesity [1]	Natural colorant in yogurts, pies, milk shakes, jams, ice creams, etc [1]	Protect human dermal fibroblasts against UV-A induced Damage [1]	[112][a 1] [113][b 1] [114][c 1]
Mulberry	Anti-oxidants, anti-atherosclerosis activity, anti-tumor activity, immunomodulatory activity, hypolipidemic activity, anti-hyperglycemic activity, neuroprotective activity [1]	Natural colorant in yogurt, ready to serve juice, wine, sake, vinegar, gelly, syrup, squash, jam, probiotics, alcoholic beverages, and chocolate [1]	Skin care, anti-aging properties[1]	[115][a 1] [116][b 1] [117][c 1]
Sour cherry	Immunomodulatory activities, anti-oxidant activities, anti-microbial activities, melatonin levels and enhanced sleep quality, anti-inflammatory activities, and anti-diabetic activities [1]	fresh fruit as well as juice, dried product, syrup, additive, and jam.[1]	Dehydration, wrinkle reduction, Anti-aging, UV irradiation, or as a cream of beauty (e.g., body care, soap, face lifting creams), and later a prescribed product can be developed against eczema and various dermatitis [1]	[118][a 1] [119][b 1] [120][c 1]
Sweet cherry	Aiding the weight loss campaign, anti-cancer, reduce arthritis, anti-inflammation, reduced muscle damage, prevent oxidative stress, against neurode-generative diseases [1]	Brined, canned, frozen, dried or juiced, jam, fruit-based beverages [1]	Skin whitening agent[1]	[121][a 1] [122][b 1] [123][c 1]
Black current	Antioxidant and anti-inflammatory activities, phytoestrogenic activity, anti-postprandialhyperglycemic and anti-diabetic, cardioprotective effect, chemoprevention, neuroprotection, cognitive improvement, vision and eye health [1]	Syrup, quick-dried black currants, vinegar, black currant honey, nectar/ juice, fresh berries, frozen berries, puree, single strength juice, freeze-dried extract powders [1]	Antimicrobial agent in cosmetics and personal care product [1]	[124][a 1] [125][b 1] [125][c 1]
Plum	Anti-oxidant, anti-cancer, anti-hyperglycemic, anti-hyperlipidemic, anti-osteoporosis, prunes are used for treatment of acid dyspepsia, nausea, vomiting, fevers, headaches, prevention of chronic degenerative changes [1]	Pickled plums, sauce, juice, liquor, condiment, or beverage [1]	Skin care and skin ageing products [1]	[126][a 1] [127][b 1] [128][c 1]
Apple	Gastrointestinal protection from drug injury, weight loss, bone health, anti-diabetes, asthma, pulmonary function, antioxidant, cardiovascular disease, anti-cancer activity [1]	Juice, wine, jams and dried product, bread, sweet bakery products (cakes, including scones and muffins), brittle bakery products (cookies and crackers), confectionery products, dairy products, using apple pomace in alcoholic beverages[1]	Anti-aging effects, regulate sebum production, relieve skin diseases such as acne, reducedermal inflammation, antioxidant [1]	[129][a 1] [130][b 1] [131][c 1]
Grape	Antioxidant, anti-inflammatory, gut microbiota modulation, anti-obesity, cardioprotective,anti-diabetic, hepatoprotective, anti-cancer, neuroprotective and anti-aging [1]	Winemaking, meat or fish products fortified with grape pomace could inhibit lipid oxidation and prolong storage or shelf life [1]	Increased cell viability, UV-A protection, UV-A photoprotection, sun protection factor booster, skin whitening, anti-ageing, and anti-acne effects [1]	[132][a 1] [132][b 1] [133][c 1]
Pomegranate	Cardioprotective, anti-oxidant, effect on blood glucose, blood pressure, blood lipids, anti-inflammatory activity, anti-viral activity, prebiotic effect, neuroprotection and improvement of the cognitive function, improvement of physical activity [1]	Alcoholic beverages, juices, jams, and jellies, canned drinks, and pastes, additive in certain foods, yogurts, seed oil [1]	Protect UV-induced hyperpigmentation, decreased skin elasticity and skin wrinkling [1]	[134][a 1] [135][b 1] [136][c 1]
Red cabbage	Anti-oxidant, hepatoprotective, cardioprotective, gout,anti-obesity, hypocholesterolemic, diarrhea, nephroprotective, neuroprotective, anti-diabetic, curing headaches and peptic ulcers [1]	Natural dye, foodstuffs, such as gummi candy, bio-based films to store cheese during refrigerated condition [1]	Collagen synthesis, strengthens skin tissues, reduction in pigmentation loss, and improved growth and health activities as a face cream [1]	[137][a 1] [138][b 1] [139][c 1]
Black carrot	Anti-microbial effect, cure vitamin-A deficiency, wound healing, ocular diseases, renal diseases, hepatic diseases, diabetes and cardiovascular diseases, anti-cancer effect[1]	Carrot pomace in cookies, wheat bread, pickle, cake, jam, ice cream, dressings, high-fiber biscuits, and production of functional drinks [1]	Skin hydration and skin elasticity, anti-oxidant, anti-inflammatory and anti-acne actions [1]	[140][a 1] [140][b 1] [141][c 1]

(*continued on next page*)

Table 3 (*continued*)

Fruits/ vegetables/ flowers	Medicinal/therapeutic uses[a]	Food supplementary[b]	Cosmetic uses[c]	References
Purple corn	Anti-oxidant properties, anti-inflammatory activities, anti-mutagenic properties, anti-angiogenesis, blood pressure regulation, heart health, obesity prevention, anti-carcinogenesis [1]	Natural colorant in acid beverages, purple corn powder making for doughs, tortillas chips using masa [1]	Anti-aging agent, anti-inflammatory and anti-acne actions [1]	[142] [a 1] [143] [b 1] [47] [c 1]
Onion	Anti-microbial, anti-tumor, anti-thrombotic, prevent hypoglycaemic and hypolipidemic, anti-arthriticproperties, immunity booster, treating running ears, cure cough, cold, flu, asthma and sour throat, anti-asthmatic properties, curing of stomach pain, remove stomach gas and bloating, preventing intestine obstructions, gastrointestinal infections, nausea and constipation, hair falls and baldness, treating jaundice in children, anti-cancer properties, anti-clotting properties [1]	Improving the quality of meat products, tea from onion peels, colorants from onion peel, packaging, oxidative stability of oils, preparation of bakery products, preparation of pasta and noodles [1]	Acne, blackheads, burns and pimples anti-inflammation on skin[1]	[144] [a 1] [145] [b 1] [144] [c 1]
Purple sweet potato	Anti-diabetic, antioxidant, antimicrobial, anti-cancer, anti-inflammatory, hepato-protective, kidney protection, anti-cancer, neuro-protective, anti-inflammatory, anti-obesity, improves intestinal health [1]	Pasta, noodles, porridge and fortified, flour, snack bar, soup, bread (orange-fleshed sweet potato flour based), cookies and cracker, fermented milk, yogurt, vinegar, juice, alcoholic beverage [1]	Skin whitening, anti-inflammation [1]	[146] [a 1] [146] [b 1] [147] [c 1]
Black beans	Anti-oxidant, diabetic, inflammatory, mutagenic, obesity, and cancer, hypercholesterolemia, and reducing the risk of coronary heart diseases [1]	Black turtle beans patties, smoky baked bean, chinese black turtle beans sauce, curry, burritos, black turtle beans soup with pork ribs [1]	Additives in anti-aging and whitening, cosmetic products, hair growth [1]	[148] [a1 & b1] [149] [c 1]
Black rice bran	Anti-diabetic, anti oxidant, anti-inflammatory,anti-cancer, weight reduction, prevention of cardio vascular diseases and anaemia, useful in gluten allergy [1]	Preparing rice wine among tribal community of Manipur, variety of Chinese and Thai dishes, kheer, porridge, bread, black rice cake [1]	Anti-aging agent [1]	[97] [a 1] [150] [b 1] [150] [c 1]
Red rice	Prevent Cardiovascular diseases, diabetes, inflammation, anti-allergy, anti-obesity, reduce hypertension [1]	Pongal, puttu, adai, appam, idli, dosai, idiyappam, adirasam, kozhukattai, modakam, payasam, semiya, uppuma, flaked rice, puffed rice	Anti-aging, hair growth-promoting,	[151] [a 1] [151] [b 1] [152] [c 1]
Hibiscus	Anti-bacterial, anti-oxidant, anti-fungal, anti-diabetic, anti-cancer, anti-fertility, neuroprotective activity, wound healing property, anti-inflammatory, gastroprotective, immune response, anti-pyritic, cardioprotective, anti-hyperlipidemic, and hepatoprotective effects [1]	Wine, juice, jam, jelly, syrup, gelatin, pudding, cakes, ice cream and flavors and also dried and brewed into tea, spice, pies, sauces, tarts, and other desserts [1]	Hairgrowth promoting activity, skin whitening, anti-aging [1]	[94] [a 1] [153] [b 1] [154] [c 1]

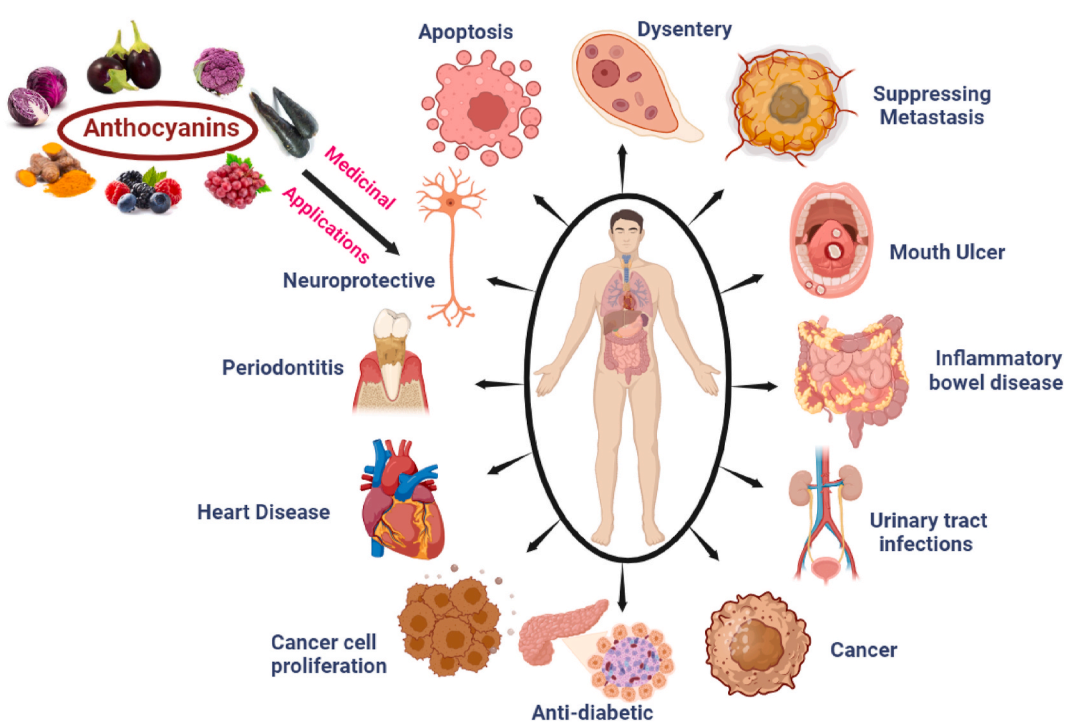

Fig. 3. A graphical depiction illustrating the diverse medical applications of ACNs (Source from www.biorender.com).

making beverages and supplements due to its perceived health benefits. Research suggests that the ACNs such as delphinidin-3-sambubioside and cyanidin-3-sambubioside are extracted from its calyx flower can effectively reduce blood pressure in both humans and rats [160]. The antioxidant properties of ACNs in the flower are believed to inhibit LDL-C oxidation, potentially slowing down the progression of atherosclerosis, a key factor in reducing cardiovascular risk. This highlights the therapeutic potential of Hibiscus sabdariffa L., in promoting cardiovascular health [161]. *Hibiscus* drink (7.5 g of *Hibiscus sabdariffa* calyx powder in 250 mL) led to a significant reduction in postprandial systolic and diastolic blood pressure. The study involved individuals aged 47–49 years with a cardiovascular risk of 1–10 %. Effects were observed after 4 h, with key contributors being phenolic compounds such as gallic acid, 4-O-methylgallic acid, and 3-O-methylgallic acid present in *Hibiscus sabdariffa* infusion (Fig. 3; Table 3) [162].

Black rice, along with its by-products and residues, is recognized for containing a substantial amount of ACNs (cyanidin-3-glucoside and peonidin-3- glucoside) [163]. Adding black rice to the daily diet can positively impact cardiovascular health by lowering triglycerides and increasing HDL ("good") cholesterol. Packed with ACNs, black rice has the potential to prevent the formation of atherosclerotic plaques, a key factor in heart attacks. Black rice also contributes to preventing arterial hardening associated with heart failure. Alongside ACNs, its dietary fiber content is linked to averting heart disease, high blood pressure, stroke, and elevated blood sugar levels, making black rice a heart-healthy dietary choice [164]. Blackcurrants (*Ribes nigrum* L.) impact resting forearm blood flow and hemodynamic variables. The effects are dose-dependent, aligning with the bioavailability of ACNs and their metabolites [165]. Grape phenolics, including red wine ACNs (cyanidin and peonidin), are associated with reduced coronary heart disease risk. Numerous studies suggest that moderate red wine consumption lowers coronary heart disease mortality. The protective effects, attributed to ACNs, involve inflammation reduction, platelet inhibition, and enhanced nitric oxide release, guarding against heart attacks (Table 3) [166,167].

5.5. Anticancer activity

ACNs play a multifaceted role in inhibiting tumors by modulating signal transduction pathways, arresting the cell cycle, and inducing apoptosis or autophagy in cancer cells. Additionally, ACNs demonstrate anti-invasion and anti-metastasis effects, reverse drug resistance, and enhance chemotherapy sensitivity. Their inhibition of cancer cell proliferation involves the regulation of anti-oncogenes and oncogenes, impacting various cell cycle regulators [3,11,168].

ACNs was evaluated in the fruit juice from different cultivars of thornless blackberries (*Rubus* sp.), blueberries (*Vaccinium* spp.), cranberries (*Vaccinium macrocarpon* Aiton), raspberries (*Rubus idaeus* L. and *Rubus occidentalis* L.), and strawberries (*Fragaria xananassa* Duch.)., with their phenolic structure, exhibit potent antioxidant activity by scavenging various reactive oxygen species (ROS) like superoxide radicals ($O^{2\bullet-}$), singlet oxygen ($'O^2$), peroxide (ROO^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH•) [169]. These effects include direct ROS scavenging, enhancement of cellular oxygen-radical absorbing capacity, stimulation of Phase II detoxification enzymes, reduction in oxidative DNA adduct formation, suppression of lipid peroxidation, and inhibition of mutagenesis by environmental toxins and carcinogens. ACNs also demonstrate metal chelation and direct protein binding and this activity diminishes with an increase in sugar moieties (Fig. 4) [170].

ACNs stimulate the activation of phase II antioxidant and detoxifying enzymes such as glutathione reductase, glutathione peroxidase, and glutathione S-transferase, alongside NAD(P)H: quinone reductase and

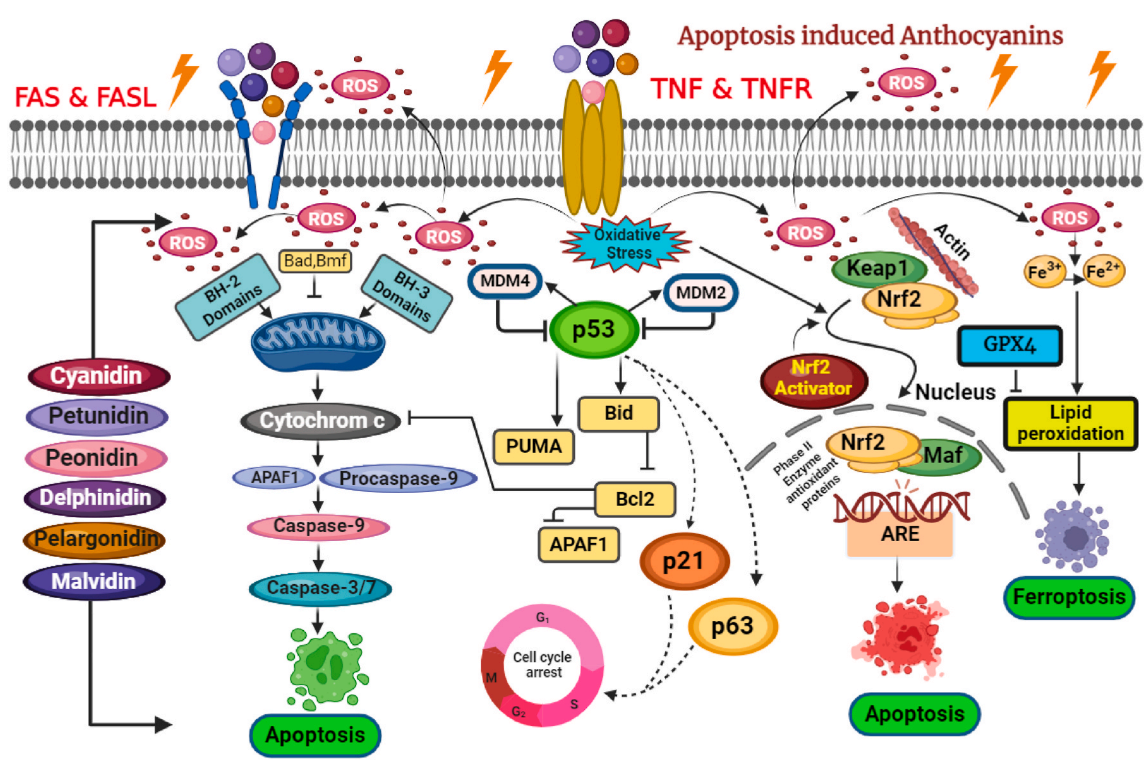

Fig. 4. The apoptotic signaling pathways encompass two main routes: one involves the interaction between ACNs receptor ligands and death receptor family membranes, particularly the FAS ligands binding to FAS to initiate apoptosis. The other pathway, induced by various stimuli such as DNA damage, triggers the activation of BH-3 proteins within the BCL-2 protein family. BH-3 proteins, in turn, inhibit apoptotic BCL-2 proteins like Bid and PUMA, resulting in mitochondrial outer membrane permeabilization. This process leads to the binding of Cytochrome-C to apoptotic peptidase activating factor 1 (APAF1), activating initiator caspase-9. Caspase-9 then cleaves and activates caspase-3/7, culminating in apoptosis. Additionally, hyperproliferative signals have a similar effect by activating p53 through disrupting the MDM2-p53 interaction. These signals may lead to cell cycle arrest by releasing the E2F transcription factor (Source from www.biorender.com).

involves the activation of the antioxidant response element (ARE) upstream of genes responsible for regulating these enzymes. ACNs enhancing the cellular defense mechanisms by regulating phase II enzyme expression, fortifying against oxidative stress [171].

ACNs extracts hinder cell proliferation by interacting with crucial cell cycle regulator proteins (p53, p21, p27, cyclin D1, and cyclin A), impeding various cell cycle stages [172]. To explore the mechanistic underpinnings of ACNs' anti-tumor properties, nine ACNs were investigated-five aglycone forms and four glycosylated forms. Their effects on cell cycle progression and induction of apoptosis in human gastric adenocarcinoma AGS cells were examined. The results from cell viability assays revealed that malvidin exhibited the most potent anti-proliferative effect on AGS cells, demonstrating both time and dose-dependent efficacy [173]. This effect coincided with the arrest of AGS cells at the G0/G1 phase induced by malvidin at varying concentrations. Moreover, anthocyanidins, particularly malvidin, played a significant role in inhibiting tumorigenesis [174]. This inhibition was attributed to the blocking of the mitogen-activated protein kinase (MAPK) pathway, specifically targeting the extracellular signal-regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways. The findings suggest a potential mechanism by which malvidin, among the tested ACNs, exerts its anti-tumor effects on human gastric adenocarcinoma AGS cells (Fig. 4) [175].

ACNs-rich extracts from berries and grapes, along with specific ACNs, exhibit pro-apoptotic effects in vitro across various cell types [176,177]. These compounds induce apoptosis through both intrinsic (mitochondrial) and extrinsic (FAS) pathways [178]. In the intrinsic pathway, ACN treatment increases mitochondrial membrane potential, triggers cytochrome *c* release, and modulates caspase-dependent anti- and pro-apoptotic proteins in cancer cells and expresses the FAS and FASL (FAS ligand) in cancer cells, promoting apoptosis [179]. Furthermore, ACN treatment induces ROS accumulation specifically in cancer cells, not normal cells, leading to apoptosis. This underscores the significance of the ROS-mediated mitochondrial caspase-independent pathway in ACN-induced apoptosis [180].

Angiogenesis is crucial for tumor growth and metastasis, driven by vascular endothelial growth factors (VEGF) often elevated in developing tumors [181]. ACNs inhibit $H_2O_2^-$ and tumor necrosis factor-alpha (TNF-α)-induced VEGF expression in epidermal keratinocytes, reduce VEGF and VEGF receptor expression in endothelial cells [11], and hinder neovascularization in the chick chorioallantoic membrane and Matrigel [182]. Treatment of mouse epidermal JB6 cells with an ACN-rich extract from black raspberries down-regulates VEGF expression by inhibiting the phosphoinositide 3-kinase (PI3K)/Akt pathway [11].

In tumor and stromal cells proteolytic enzymes must be secreted for the successful intravasation of tumor cells [183,184]. The balance between activated proteases and their inhibitors is crucial for basement membrane degradation, with matrix metalloproteinases (MMP) and plasminogen activators playing a key regulatory role [185,186]. The extraction of berries, black rice, and eggplants reduce the expression of MMP and urokinase-plasminogen activator (u-PA), responsible for extracellular matrix degradation during invasion. Additionally, they stimulate the expression of tissue inhibitor of matrix metalloproteinase-2 (TIMP-2) and inhibitor of plasminogen activator (PAI), countering the actions of MMP and uPA [186,187].

ACNs positively influence mesenchymal stem cell differentiation into osteoblasts and promote cell proliferation. ERK1/2, a key player in the MAPK cascades, serves as a positive regulator for osteoblast differentiation and bone formation. Research study investigated the impact of cyanidin-3-glucoside treatment significantly increased osteoblast mineralization via the ERK1/2 pathway, validated in primary osteoblasts and MC3T3-E1 cells. C3G enhanced osteoblast proliferation, mineralization points, mRNA, and protein expression of osteocalcin (OC). Increased ERK phosphorylation by C3G was inhibited by an ERK pathway inhibitor. These findings suggest C3G's potential in osteoporosis strategies via ERK-mediated osteoblast modulation (Fig. 4) [188].

5.6. Other biological activities

Recent research has unveiled novel biological activities of ACNs, beyond their recognized ones. Notably, some studies have illuminated their potential in modulating gut microbiota composition and function, thereby influencing gastrointestinal health. ACNs have shown promise in mitigating neurodegenerative diseases by targeting pathways involved in neuroinflammation and oxidative stress, suggesting a potential role in neuroprotection. Furthermore, emerging evidence indicates their ability to enhance skeletal muscle function and metabolism, hinting at potential applications in sports nutrition and age-related muscle wasting conditions. These findings underscore the multifaceted biological effects of ACNs and highlight avenues for future exploration in both preventive and therapeutic interventions.

5.7. Food industry

The applications of natural ingredients in the food industry is rather widespread as exemplified by cranberries, which enhances beverages and dairy products [102], blackberries, which add versatility to desserts and beverages [105], mulberries, which showcase significant potential across various food products, and grapes, which contribute to diverse applications in food manufacturing (Fig. 5) [116]. They underscore the crucial role of color as a quality parameter in the food industry and explores the utilization of ACNs, particularly from red cabbage, as natural colorants. Cranberries, and particularly their powder extract, can be considered as novel food containing 55–60 % proanthocyanidins, are designed for use in diverse beverages and dairy products to augment them with 80 mg of proanthocyanidins per serving. This application spans a variety of drinks, including fruit-flavored beverages, isotonic beverages, low-calorie fruit-flavored drinks, ready-to-drink iced tea, and vitamin waters. Moreover, the powder is well-suited for incorporation into milk and various dairy items like yogurts and yogurt drinks, offering a means to elevate their nutritional content with the beneficial bioactive compounds found in cranberry extract powder [102].

ACNs from blackberries are used fresh and as prepared items of food

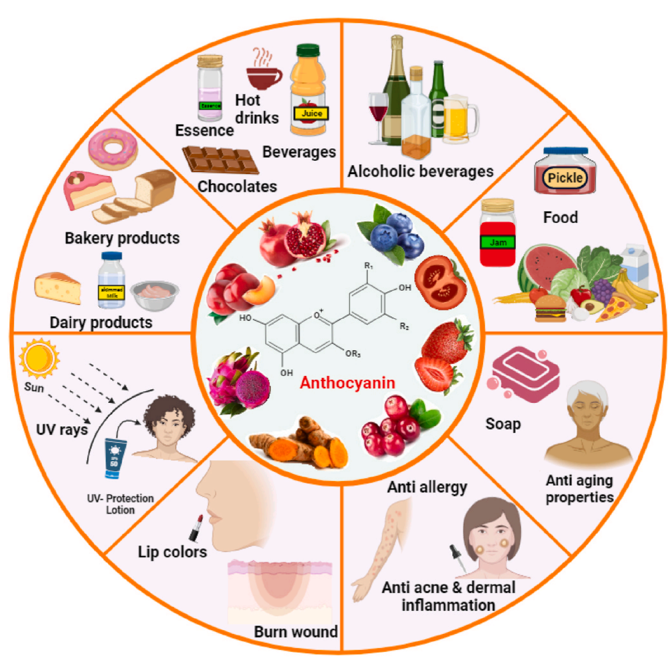

Fig. 5. The utilization of ACNs in both food and cosmetic sectors (Source from www.biorender.com).

e.g. desserts, yogurt, jams, wine, syrups and jellies. The flowers of blackberry are good producers of nectar which can yield fruity honey. The ripened fruits of the blackberry can be eaten uncooked or cooked and can also be used to prepare juice, liqueurs, jams and wine [105]. ACN rich mulberry (*Morus* spp.) presents significant potential in the fruit and vegetable industries, offering versatile applications in the production of marmalade, fondant, jams, jellies, cakes, breads, parathas, fruit teas, pulp drink, wine, sauce, powder, and chocolate. This exploitation is attributed to the fruit's high sugar content. Mulberries, whether in dried, frozen, or fresh forms, are employed in the food industry for the extraction of diverse products, including syrups, amaretto or vermouth wine, tonic wine, and vinegar. Persian culinary practices involve the utilization of mulberries in the creation of jellies, desserts, and sauces. The juice derived from mulberries contributes to skin health, offering preventative measures against irritations, inflammations, and throat infections. In Iranian culture, dehydrated mulberries are incorporated as a sweetening agent in black tea (Table 3) [116].

The food industry uses ACNs extracted from grapes as natural food colorants and food additives. The main source of ACNs for food colorants is the skins of grapes and it is consumed as fresh fruit and finds various products derived from grapes are manufactured and available in the market, including wine, grape juice, grape jam, and raisins. Moreover, research indicates that incorporating grape pomace into meat or fish products may effectively inhibit lipid oxidation, extending storage or shelf life [132].

Strawberries stand as a pivotal seasonal fruit crop, prized predominantly for their fresh consumption. However, due to their limited shelf life and seasonal availability, a portion of the harvest undergoes processing. This processing serves for various purposes, including extending shelf life and facilitating integration into a wide array of food products such as yogurts, pies, milkshakes, jams, and ice creams. These applications capitalize on the fruit's appealing sensory characteristics. The prevalent methods employed in strawberry processing include freezing, partial or total dehydration, and combinations thereof. However, these processes inevitably induce alterations in sensory attributes such as texture and color, as well as modifications in the profile of volatile compounds. Consequently, the processed strawberry products exhibit discernible differences from their untreated counterparts [113].

ACNs from red cabbage, as an inherent quality indicator, play a critical role in detecting physicochemical changes. Advancements in intelligent color sensors and labels contribute to enhanced product safety monitoring [189]. The preference for natural colorants, especially those derived from plants, surpasses the use of synthetic dyes. ACNs, being water-soluble phenolic compounds, offer a variety of colors and demonstrate sensitivity to environmental changes. Investigated for use in smart packaging responsive to pH, gas, or temperature, ACNs facilitate real-time monitoring throughout the shelf life. Research into their potential for smart packaging is challenging, as they enable real-time monitoring of pH, gas levels, and temperature, ensuring food quality maintenance throughout storage. Their standout features lie in their reversible color alteration in response to pH fluctuations, making them an ideal tool for precise food quality tracking. Red cabbage serves as a valuable example, and its ACN content serve as a reliable indicator of freshness and integrity in food products [190]. However, safety concerns, heightened consumer awareness, and the availability of natural colorants propel the demand for plant-derived extracts [3].

5.8. Cosmetic uses

The term "return to nature" has been extensively used in cosmetic industry research and development, as the use of extracts of botanical origin has resulted in good acceptance by consumers. Blueberries, chokeberries, mulberries, plum, apples, grapes, purple corns possess a rich concentration of ACNs, specifically delphinidin and malvidin. These bioactive constituents endow blueberries with notable antioxidant properties, complemented by the presence of vitamins, minerals, and resveratrol. Beyond their anti-aging attributes, ACNs play a pivotal role in enhancing the photoprotective potential of formulations. Cosmetic formulations, that incorporate microparticles, demonstrate heightened physical stability. The inclusion of blueberries not only amplifies the photoprotective efficacy of these formulations but also imparts supplementary advantages attributed to its antioxidant and anti-aging attributes. This synergistic interaction underscores the pivotal role of blueberries in advancing skin health and fortification within the realm of cosmetic applications (Fig. 5) [105,109,133].

Lipstick, a widely used cosmetic product, provides social, psychological, and therapeutic benefits but can pose harm due to high lead levels in some formulations. Research suggests antioxidants can counter lead's toxic effects. *Hylocereus polyrhizus* (Red dragon fruit) in Myanmar, rich in the antioxidant betacyanin pigment, may counter oxidative stress caused by lead, making it suitable as a natural lipstick colorant. This study aimed to formulate a safer lipstick using betacyanin from *H. polyrhizus* and other natural ingredients. Successful formulations demonstrated color stability, antioxidant ability, UV protection, melanin inhibition, and dermal penetration, offering a healthier alternative. The use of ACN sources with reported stability and health benefits proved effective, showcasing a broad spectrum of colors and exceeding two years of shelf stability under accelerated testing [191].

Blackberries have been used several times to dye fabrics as well as hair dye. Despite containing a rich array of bioactive compounds, their complete utilization remains underexplored. Blackberry ACNs show cosmeceutical properties, with documented anti-aging effects and skin whitening [177]. Additionally, ACNs extracts from apples demonstrated inhibitory effects on sebum production in sebaceous cells in vitro, suggesting a potential regulatory role in addressing skin conditions like acne and reducing dermal inflammation. The diverse bioactivity of these compounds highlights their potential for broader applications in cosmetics and dermatology [131].

ACN extracts from grapes have been shown to prevent and alleviate skin degradation caused by UV radiation, a cumulative process affected by the frequency, duration, and intensity of solar exposure, along with the natural protection offered by skin pigmentation [192]. It is crucial to underscore that the impact of both types of aging factors becomes especially notable in the presence of oxidative stress. Strategies such as inhibiting skin-degrading enzymes, safeguarding against UVA damage, boosting cell viability, and fostering a skin-whitening effect play pivotal roles in addressing these concerns (Fig. 5; Table 3) [133].

6. Conclusions

In conclusion, ACNs, hydrophilic pigments within the flavonoid group, stand out as remarkable compounds found in a variety of fruits, vegetables, and flowers. The distinct ACN profiles in different plant sources, coupled with advanced extraction and purification techniques, allow for a comprehensive understanding of these compounds, crucial for both analytical and nutritional perspectives. Their diverse health benefits, ranging from potent antioxidant and anti-inflammatory properties to potential therapeutic applications in preventing urinary tract infections, diabetes, cardiovascular issues, and cancer, underscore their versatility in promoting human health. In addition, ACNs reflect a significant trend in the food and cosmetic industries. This shift not only enhances sensory attributes such as flavor and color but also aligns with consumer preferences for healthier and more sustainable options. Overall, the scientific evidence presented highlights the pivotal role of ACNs in fostering a comprehensive and preventative approach to health, contributing to a broader movement towards sustainable and health-conscious practices.

Prospects and future research in the anthocyanin field

Research on ACNs primarily focuses on understanding their diverse applications and benefits. This includes exploring their roles in human health, such as their antioxidant properties and potential in preventing diseases like cancer and cardiovascular issues. Additionally, there is an ever-increasing interest in their use in the food and beverage industries for color enhancement and functional properties. Future research aims to uncover new sources, improve extraction methods, and develop innovative technologies for their utilization across various sectors, advancing both health and industry.

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CRediT authorship contribution statement

Mythileeswari Lakshmikanthan: Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Sakthivel Muthu:** Writing – original draft, Visualization, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Kathiravan Krishnan:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Ammar B. Altemimi:** Writing – review & editing, Data curation. **Noor N. Haider:** Writing – review & editing. **Lakshmanan Govindan:** Writing – review & editing, Conceptualization. **Jeyaperumal Selvakumari:** Writing – review & editing, Conceptualization. **Zina.T. Alkanan:** Writing – review & editing. **Francesco Cacciola:** Writing – review & editing, Supervision, Data curation. **Yuvaraj Maria Francis:** Writing – review & editing, Project administration.

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

Data will be made available on request.

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