



Barberry (*Berberis vulgaris*): Exploring its nutritional composition, bioactive components, and health benefits for humans

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ABSTRACT

Berberis vulgaris L. (barberry), a member of the Berberidaceae family, has been widely utilized in traditional medicine for over 2500 years and is increasingly recognized for its pharmacological properties. This review aims to evaluate the nutritional and phytochemical profile of *B. vulgaris*, synthesize evidence for its health benefits across preclinical and clinical studies (2003–2025) using PubMed/MEDLINE, ScienceDirect, Scopus, Web of Science, clinical trial registries, and identify gaps in current research to guide future investigations. Our hypothesis says that *B. vulgaris* exerts multisystem therapeutic effects primarily through its high berberine and polyphenol content, which modulate oxidative stress, inflammation, and metabolic pathways. The fruit, leaves, roots, and bark of *B. vulgaris* contain a diverse array of bioactive compounds, including alkaloids (e.g., berberine), anthocyanins (e.g., cyanidin-3-glucoside), phenolic acids (gallic acid, chlorogenic acid), flavonoids (quercetin, myricetin), and essential minerals (Ca, K, Fe, Zn). Pharmacological studies demonstrate significant ($p < 0.05$) antioxidant capacity (88.9 % radical scavenging), *in vitro* and *in vivo* anticancer effects (apoptosis induction in breast, colon, liver cancer cells; $p < 0.05$), anti-inflammatory (30–68 % edema inhibition; $p < 0.05$), antimicrobial (ZOI: 6–19 mm against *S. aureus*, *E. coli*; $p < 0.05$), and gastro-protective (74.81 % ulcer reduction; $p < 0.05$) effects. Clinical trials confirm its efficacy in managing metabolic syndrome, reducing low density lipoprotein-cholesterol ($p < 0.05$), and improving glycemic control in type 2 diabetes ($p < 0.05$). This review specifically addresses the existing gap in correlating phytochemical diversity with mechanistic and clinical outcomes, highlighting the need for standardized extraction methods and enhanced bioavailability strategies. Overall, *B. vulgaris* emerges as a promising nutraceutical and therapeutic candidate, warranting further long-term clinical validation to establish its safety and efficacy.

Abbreviations: BAR, Barberry; BAR_F, Barberry fruit; AxAc, Antioxidant Activity; TACy, Total Anthocyanin Content; TPC, Total Phenolic Content; GAE, Gallic Acid Equivalents; DW, Dry Weight; FW, Fresh Weight; CAT, Catechin; QE, Quercetin Equivalents; PE, Pyrogallol Equivalents; NO, Nitric oxide; DPPH, 2,2-Diphenyl-1-picrylhydrazyl; FRAP, Ferric Reducing Antioxidant Power; ABTS, 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); ORAC, Oxygen Radical Absorbance Capacity; IC₅₀, Half-Maximal Inhibitory Concentration; ZOI, Zone of Inhibition; MIC, Minimum Inhibitory Concentration; MDA, Malondialdehyde; TNF- α , Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; TGF- β 1, Transforming Growth Factor Beta 1; HSP, Heat Shock Protein; hs-CRP, High-Sensitivity C-Reactive Protein; FMD, Flow-Mediated Dilation; ICAM-1, Intracellular Adhesion Molecule-1; MCP-1, Macrophage/Monocyte Chemoattractant Protein-1; GC-MS, Gas Chromatography-Mass Spectrometry; LC-MS, Liquid Chromatography-Mass Spectrometry; HPLC, High-Performance Liquid Chromatography; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein.

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1. Introduction

Berries are rich in bioactive compounds such as polyphenols, flavonoids, vitamins, and minerals that contribute to human health. Recent studies highlight their antioxidant, anti-inflammatory, and cardioprotective effects [1]. Similarly, *Berberis vulgaris*, commonly known as barberry (BAR), also known as Zerezhk [2] is a plant that belongs to the Berberidaceae family, comprising of 500 species around the globe [3]. This thorny shrub (1–3 m tall) has prickly yellow wood, oblong leaves, yellow flowers in pendant clusters (10–20 per panicle), and produce rectangular red fruits. Its asexual, glossy flowers, and reddish-brown barberry fruit- BAR_F (up to 13 mm) complete its distinct morphology [4,5]. *Berberis* species are native to Europe, Asia (including northern Iran and Pakistan), northeastern U.S. and northwest Africa [6, 7]. Iran is the largest global producer of BAR_F, with a vast expanse of 11, 000 ha of cultivated land dedicated to its growth, producing approximately 10,000 tons of dried BAR_F annually. The majority of BAR cultivation, accounting for >97 % of all land, is concentrated in the Ghaenat region, which is located in the Southern Khorasan province of Iran [8]. BAR anatomical parts has been used in herbal medicine since ages to manage fever, digestive disorders (diarrhea, dysentery, indigestion), inflammatory conditions (rheumatism, gout, wounds, skin diseases), metabolic diseases (diabetes, icterus, kidney stones), neurological issues (Alzheimer's disease, depression), reproductive ailments (uterine and vaginal disorders), toxic exposures (snake or scorpion injury), as well as piles, hemorrhoids, hypertension, liver diseases and purification of blood [4,6,9–12]. To alleviate acrid urine or excruciating micturition caused by bilious, a decoction of BAR and *Emblis myrobalan* mixed with honey is recommended [4]. These traditional medicinal claims are well supported by pharmacological properties such as antihypertensive, anti-inflammatory, antioxidant, anticancer, antimicrobial, and hepatoprotective properties [4,13–15], believed to be due to the existence of alkaloids, flavonoids, and phenolic acids [16]. The Food and Drug Administration has approved the use of BAR_F for human consumption [17]. BAR contains a wide variety of bioactive compounds in various BAR parts [18]. Berberine, the primary active alkaloid, is present in all parts of BAR, with a benzyl tetra hydroxy quinoline chemical structure, particularly in the fruit [17]. However, current research on BAR lacks standardized methodologies and robust clinical validation, despite its long-standing traditional use and demonstrated bioactivity. This review consolidates existing evidence to clarify its therapeutic potential and guide future research.

2. Methodology

This review synthesizes evidence for *B. vulgaris* anatomical parts health benefits across preclinical and clinical studies (2003–2025) using PubMed/MEDLINE, ScienceDirect, Scopus, Google Scholar, Web of Science, and clinical trial registries using keywords: “Barberry fruit,” “*Berberis vulgaris*,” “Zerezhk,” “berberine,” “minerals in *B. vulgaris*,” “traditional medicinal uses of *B. vulgaris*,” “biological potential of *B. vulgaris*,” “antioxidant activity of *B. vulgaris*,” “*in vitro* and *in vivo* anti-inflammatory of *B. vulgaris*,” “hypertension and *B. vulgaris*,” “dyslipidemia and *B. vulgaris*,” antimicrobial activity of *B. vulgaris*,” “anticancer activity of *B. vulgaris*,” and “clinical trials and *B. vulgaris*”. Moreover, conference abstracts, letters to the editors, proceedings of conferences, literature reviews, meta-analyses were excluded from the study.

3. Nutritional profile of *B. vulgaris* fruit

BAR is a plethora of bioactive micro- and macronutrients that are beneficial for health. The composition of BAR_F is 1.16 % fat, 2.00 % protein, 16.24 % carbohydrate, and 0.99 % ash, with a moisture content of 79.6 % [19]. The nutritional composition of three distinct varieties of BAR_F, BVF01, BVF02, and BVF03, from the regions of Azad Kashmir, Chitral, and Gilgit Baltistan, was approximated to be 77.43, 70.08, and

73.12 % for moisture; 0.98, 0.76, and 0.89 % for crude ash; 0.42, 0.33, and 0.39 % for crude fat; 1.53, 1.32, and 1.44 % for crude protein; 2.76, 2.64, and 2.75 % for crude fiber; and 16.88, 24.87, and 21.41 % for nitrogen-free extract (NFE) [2]. Ardestani et al. [20] demonstrated that BAR_F contains moisture (75 %), ash (0.74 %), fat (0.62 %), fiber (2.62 %), protein (0.12 %), total sugar (9.48 %), and acidity (2.63 % malic acid). BAR_F contains 3.02–0.22 IU/kg of vitamin A, and 776.86–39.19 IU/kg of vitamin E [21]. The vitamin C content of BAR_F is 11.0103 µg/100 g [22,23]. A concentration of 5.2–7.7 % berberine was detected in BAR_F. The BAR root extract contained 0.73 mg/mL of berberine, as determined by Ref. [24].

3.1. Minerals in *B. vulgaris* fruit

The nutritional abundance of BAR_F and its potential to promote good health are emphasized by the presence of minerals, which encompass both trace elements and essential nutrients (Table 1).

Calcium is important for bone health and muscle function [30]. Potassium regulates blood pressure and promotes cardiovascular health [31]. Magnesium is involved in neuronal function, muscle relaxation, and energy metabolism [32]. Iron is necessary for the transportation of oxygen in the blood and for maintaining overall energy levels [33]. Zinc plays a crucial role in enhancing immunological function, wound healing, and DNA synthesis [34]. Copper is involved in antioxidant defenses and collagen production of collagen [35]. It can be seen in Table 1 that all aforementioned minerals are present in *B. vulgaris* fruits in a notable amount followed by leaves and roots. In addition, lower amounts of trace elements, including Ag, Al, As, boron, and Ba, have also been found in BAR_F [18,24].

3.2. Phytochemicals composition of *B. vulgaris*

Phytochemicals are bioactive compounds naturally present in plants and are responsible for a variety of biological activities and health benefits [36]. Table 2 presents the phytochemical composition of BAR fruits, leaves, roots, and stems. Table 3 provides comprehensive information on the bioactive compounds found in different parts of BAR.

Total anthocyanin content (TAC) was highest in fruit extracts prepared using ethanol (785 mg cy-3-glu/L) [37], while total phenolic content (TPC) varied widely across studies, with values of 2617 mg GAE/100 g FW reported by Okatan and Çolak [5]. Leaves extracted with ethanol showed high phenolic and flavonoid contents, revealing its potential for antioxidant activity (A_{XAc}). Similarly, roots displayed substantial phenolic compounds when extracted with ethanol [14]. Stem extracts prepared using methanol revealed moderate levels of phenols, flavonoids, and tannins [43]. Hanachi and Golkho [22] found 20.51 µg/100 g tannins in BAR_F. These findings highlight the diversity of phytochemicals present in different parts of the BAR and underscore the importance of solvent selection in determining the bioactive profile. Importantly, differences in extraction techniques (e.g., solvent polarity, temperature, extraction time, and plant part used) lead to variation in the yield and profile of bioactive compounds such as alkaloids, flavonoids, and phenolic acids. This variability limits the reproducibility and comparability of biological outcomes across studies.

4. Pharmacological potential of *B. vulgaris*

The World Health Organization (WHO) has estimated that 80 % of the Earth's inhabitants rely on traditional medicine for their primary healthcare needs, and most of this therapy involves the use of plant extracts and their bioactive [48]. The fruit, leaves, seed, root extracts, and bioactives of BAR demonstrated exceptional potential to inhibit the generation of free radicals, inflammation, growth of cancer cells, pathogenic bacteria, and a variety of other ailments. These findings substantiate the claims regarding BAR in ancient medicinal plants. The subsequent sections examined the pharmacological activity of BAR that

Table 1
Minerals composition of various anatomical parts of *B. vulgaris*.

Mineral	Fruit					Leaves		Roots		Shoot
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kg	µg/g	µg/g	µg/g	µg/g	µg/g
Ag	41.73	46.21	–	–	–	–	–	0.000044	–	–
Al	16.86	17.68	–	–	–	–	–	–	–	–
As	3.54	4.64	–	–	–	3	–	–	–	–
B	56.93	63.23	–	–	–	38	–	–	–	–
Ba	1.42	1.58	–	–	–	17	–	–	–	–
Bi	0.22	0.26	–	–	–	–	–	–	–	–
Ca	2744	2439	2694	–	–	11130	2389	–	543	941
Co	0.26	0.31	–	–	–	–	–	–	–	–
Cr	33.21	37.13	–	–	–	–	–	0.00004	–	–
Cu	4.75	4.85	11.63	33.7	–	327.393	53.41	–	95.67	15.8
Fe	323.86	320.36	396.90	2650	198.1	95	528	–	352.23	492.33
K	12,111	11,216	12,021	–	–	7857	4077	–	2458	5824
Li	0.32	0.43	–	–	–	–	–	–	–	–
Mg	1193.30	1123.10	986.32	–	–	1777	–	–	–	–
Mn	6.54	6.60	28.91	58.6	–	41	136	0.00003	27.86	73.54
Na	2569	2498	1269	–	–	589	79	–	115	125
Ni	19.98	21.24	–	–	–	–	–	–	–	–
P	2716	2536	–	–	–	4	1315	–	451	563
Sr	16.17	19.46	–	–	–	–	–	–	–	–
V	0.69	0.88	–	–	–	–	–	–	–	–
Zn	7.95	8.97	29.5	27.5	45.3	14	37	0.00004	56.15	38.74
	[18]	[24]	[2]	[25]	[26]	[27]	[28]	[29]	[28]	[28]

Table 2
Phytochemical compositions of various anatomical parts of *B. vulgaris*.

Plant part	Extraction solvent	Total anthocyanins	Total phenolic content	Total flavonoids	Total tannin content	References
Fruit	Water	602 mg cy-3-glu/L	184.1 mg GAE/g DW	Nd	Nd	[37]
	Ethanol	785 mg cy-3-glu/L	291.22 1 mg GAE/g DW	Nd	Nd	
	Acetone	Nd	92.75 mg GAE/g	–	Nd	[38]
	Ethanol	Nd	2616.78 mg GAE/100 g FW	965.97 mg CAT/100 g FW	Nd	[5]
	Ethanol	39.6 mg cy-3-glu/L	51.3 mg GAE/mL	Nd	Nd	[39]
		Nd	448.3 µg GAE/mg	Nd	Nd	[40]
	Water	Nd	337.1	Nd	Nd	
	Methanol	22.81 %	94.04 mg GAE/100 mL	76.70 mg QE/100 mL	18.50 µg CAT/mL	[41]
	–	Nd	Nd	Nd	20.51 µg/100g	[36]
	Ethanol	Nd	120.7 mg GAE/g	59.58 mg QE/g	Nd	[14]
Leaves		Nd	147.2 mg GAE/g	24.15 mg QE/g	Nd	
Root		Nd	28.92 mg GAE/g	0.56 mg QE/g	Nd	[42]
Fruit	Water	Nd	789.32 mg/kg	Nd	Nd	[18]
	–	931.05 mg/kg	28.0 g/100 g	Nd	Nd	[20]
	Ethanol	69.01 g/100 g	19.54 g/100 g	Nd	Nd	
Stem	Water	62.10	57.7 mg GAE/g	4.6 mg QE/g	4.5 mg PE/g	[43]
Leaves	Methanol	–	58.5 mg GAE/g	15.3 mg QE/g	4.6 mg PE/g	
Fruit			52.8 mg GAE/g	6.1 mg QE/g	17.1 mg PE/g	

mg cy-3-glu: mg cyanidin-3-glucoside, mg GAE/g: mg gallic acid equivalents per gram; DW: dry weight; FW: fresh weight; mg CAT/100 g FW: mg catechin per 100 g fresh weight; mg QE/100 mL: mg quercetin equivalents per 100 mL; mg PE/g: mg pyrogallol equivalents per gram.

have been documented.

4.1. Antioxidant activity

During aerobic metabolism, living systems produce reactive oxygen/nitrogen species (ROS/RNS). Oxidative stress arises from an imbalance between ROS and the body’s antioxidant defenses, contributing to disease development. Antioxidants counteract this by inhibiting free radical formation, scavenging ROS, chelating metal ions, and reducing hydrogen peroxide and superoxide levels as depicted in Fig. 1 [49]. A_xA_c of BAR has been evaluated by different researchers using different *in vitro* assays (Table 4), including nitric oxide (NO), 2,2-diphenyl-1-picrylhydrazyl (DPPH), ferric reducing antioxidant power (FRAP), 2, 2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and oxygen radical absorbance capacity (ORAC) [37,38,50,51]. Among the aqueous and ethanolic extracts of BAR_F, the ethanolic extract (5 mg/mL) showed the highest A_xA_c, that is, 88.9 % against DPPH radical, attributed to its greater TAC (785 mg cy-3-glu/L) and TPC (291 GAE/g dw) [37].

BAR_F methanol extract exhibited A_xA_c in DPPH (60.23 %), FRAP

(60.29 TE mmol/L), and Fe²⁺ chelating activities (31.44 %). Furthermore, it increased the activity of antioxidant enzymes: guaiacol peroxidase (G-POD) to 29.88 DA/mg protein, superoxide dismutase (SOD) to 23.2 U/mg protein, and catalase (CAT) to 36.13 [51]. A_xA_c of BAR_F extracts in acetone, ethanol, and water (infusion and decoction) was studied using the ABTS, DPPH, and reducing power methods. The results showed that BAR_F extracts in acetone and decoction could be used as effective natural antioxidants in the food industry [38]. In 2019, a study was conducted on the phytochemical values of 16 distinct BAR genotypes collected from the Sivash district of Uşak province in Western Turkey. The results of the study indicated that the total flavonoids in BAR ranged from 262 to 966 mg CAT/100 g FW, with the highest ascorbic acid concentrations at 444.35 mg/100 g and the lowest at 120 mg/100 g. TPC (1199–2617 mg GAE/100 g FW) and A_xA_c (126–34 %) of the various genotypes were found to vary [5].

The methanol extract of BAR_F showed an A_xA_c of approximately 8.731 µmol trolox equivalent (TE)/g, as evaluated by the ABTS assay [25]. A_xA_c of BAR roots and leaves were assessed at concentrations of 18.7 and 14.7 g/100 g, respectively. The results suggested that the roots

Table 3
Bioactive compounds identified in various anatomical parts of *B. vulgaris*.

Plant part	Analysis	Class/name of compound	Ref.
Fruit	GC-MS;	Polyphenols: Gallic acid, Protocatechuic acid, 5-Caffeoylquinic acid, 4-Caffeoylquinic acid, Caffeic acid, Catechin, Luteolin, Quercetin, Eriodictyol, Eriodictyol-7-glucopyranoside, Rutin, Hyperoside, Isoquercetin, Quercitrin, Afzelin, Narcissoside, Isorhamnetin-3-glucoside, Naringenin 7-glucoside Terpenoids (Terpenes): α -Ylangene, α -Longipinene, α -Curcumene, α -Bulnesene, Aromadendrene oxide, α -Guaiene, cis-5,8,11,14,17-Eicosapentaenoic acid Alkaloids: Berberine Organic Acids: Acetic acid, Propanal, Octadecanoic acid, 3-hydroxy-, methyl ester, Butyric acid, Caproic acid, Undecanoic acid, Lauric acid, Myristic acid, Palmitic acid, Heptadecanoic acid, Oleic acid, Linoleic acid, Arachidic acid, α -Linolenic acid, cis-11-Eicosenoic acid, Behenic acid, Eicosapentaenoic acid, Lignoceric acid, Palmitic acid, vaccenic acid, 9,12-Octadecanoic acid (z, z), Tetradecanoic acid, Hexadecanoic acid methyl ester, <i>n</i> -Hexadecanoic acid, Tetracosanoic acid, Methyl ester Other: Phenylethyl Alcohol, Ribitol, 3-(2-Hydroxyphenyl) acrylic acid, 6-Nonynoic acid, Benzyl alcohol, Benzene, 1,3,5-Trimethyl-, Phenol, 2-Methoxy, α -Sesquisabinene hydrate, 2-Methoxy-4-vinylphenol, trans-Sesquisabinene hydrate	[26,42, 44]
	LC-MS		
Leaves	LC-MS	Fatty Acid Methyl Esters: Dodecanoic acid, Lauric acid, Tetradecanoic acid, Myristic acid, Hexadecanoic acid, Palmitic acid, Octadecanoic acid, Stearic acid, 9-Octadecanoic acid, Oleic acid, 7,10,13-Hexadecatrienoic acid, Palmitoleic acid, 9,12-Octadecadienoic acid, Linoleic acid, 9,12,15-Octadecatrienoic acid, Linolenic acid, Tetracosanoic acid, Lignoceric acid Phenolic Acids: Gallic acid, Chlorogenic acid, Rosmarinic acid, Syringic acid, <i>p</i> -coumaric acid, Ferulic acid, <i>O</i> -coumaric acid, Protocatechuic acid, Caffeic acid, Vanillic acid Flavonoids: Catechin, Apigenin, Luteolin, Kaempferol, Rutin, Myricetin, Quercetin, Eriodictyol, Eriodictyol-7-glucopyranoside, Hyperoside, Isoquercetin, Quercitrin, Afzelin, Narcissoside, Isorhamnetin-3-glucoside, Naringenin 7-glucoside, Luteoloside Phenolic Compound: 4-Vinylguaiacol Carbohydrate: D-Mannoheptulose Heterocyclic Compound: Benzothiazole, 2-methyl	[14,42, 43,45]
Wood	GC-MS	Fatty Acid: Tetradecanoic acid Phthalate Ester: Di-(2-ethylhexyl)phthalate Anthraquinone Derivative: 1-Amino-2-(hydroxymethyl)anthraquinone Aldehyde: Benzaldehyde Aromatic Amine Derivative: 2-[(1-(2-aminophenyl)methylidene] amino)phenyl)methylidene]amino} Phthalate Ester: 1,2-Benzenedicarboxylic acid, diisooctyl ester, 1,2-Benzenedicarboxylic acid, diisononyl ester Fatty Acid Methyl Ester: Tetracosanoic acid Oxetane Derivative: 2-(4-Methylphenyl)-3-(1-hydroxyhexyl)oxetane Benzoxepin Derivative: 2H-3,9a-Methano-1-benzoxepin, octahydro-2,2,5a,9-tetramethyl-, [3R(3 α ,5 α ,9 α ,9 α)] Ketone: Phenyl(1-phenyl-3,3-dimethylbutyl)	[46]
Inner bark	GC-MS		[46]

Table 3 (continued)

Plant part	Analysis	Class/name of compound	Ref.
Root	HPLC	ketone Sesquiterpene Oxide: Epi-ligulyl oxide Phenolic Acids: Gallic acid, Chlorogenic acid, Rosmarinic acid, Syringic acid, <i>p</i> -coumaric, Ferulic acid, <i>O</i> -coumaric, Caffeic acid, Vanillic acid Flavonoids: Rutin, Quercetin, Myricetin, Kaempferol, Luteolin, Apigenin, Catechin Alkaloids: Tetrahydroberberine, Berberine, Reticuline Other Categories: Guaijaverin, Prothocatechuic acid, Resorcinol	[14,47]
		Phenolic Acids: Gallic acid, Protocatechuic acid, Caffeic acid Chlorogenic Acids: 3-caffeoylquinic acid, 5-caffeoylquinic acid, 4-caffeoylquinic acid Flavonoids: Catechin, Luteolin, Quercetin, Eriodictyol, Rutin, Hyperoside, Luteoloside, Isoquercetin, Quercitrin, Afzelin Other Categories: Eriodictyol-7-glucopyranoside, Eleutheroside E	
Stem	LC-MS	Phenolic Acids: Gallic acid, Protocatechuic acid, Caffeic acid Chlorogenic Acids: 3-caffeoylquinic acid, 5-caffeoylquinic acid, 4-caffeoylquinic acid Flavonoids: Catechin, Luteolin, Quercetin, Eriodictyol, Rutin, Hyperoside, Luteoloside, Isoquercetin, Quercitrin, Afzelin Other Categories: Eriodictyol-7-glucopyranoside, Eleutheroside E	[43]

GC-MS, Chromatography-Mass Spectrometry. LC-MS, Liquid Chromatography-Mass Spectrometry. HPLC, High-Performance Liquid Chromatography.

demonstrated greater activity in both the DPPH assay (44.3 %) and ABTS assay (86.5 %) than leaves [14]. The BAR ethanolic extract exhibited higher A_{XAC} values of 40.44 % for DPPH and 76.54 % for ABTS than aqueous extract [40].

The A_{XAC} of the BAR samples collected from three distinct areas in China was evaluated using β -carotene bleaching. The BAR_F extract from Jilin province demonstrated a maximum A_{XAC} of 92.34 %, followed by Heilongjiang at 68.23 % and Liaoning at 71.45 % [24]. BAR_F ethanolic extract was reported to have A_{XAC} against DPPH with an IC_{50} = 88.0 μ g/mL [39]. The BAR methanolic extract also exhibited A_{XAC} against DPPH (56.84 %) [41]. Gidik [42] reported that ethanolic BAR_F extract exhibited SC_{50} 0.10 mg/mL for DPPH and 621 μ mol FeSO₄.7H₂O/g for FRAP. Root bark ethanol and ethyl acetate extracts possessed synergistic A_{XAC} against DPPH radicals with IC_{50} = 69.65 and 77.75 μ g/mL, respectively [52]. Och et al. [43] studied A_{XAC} of BAR leaves, fruit, and stem and revealed the highest activity of fruit and leaf extracts owing to the highest amount of polyphenols in these extracts. Hydro-ethanolic BAR stem bark extract was reported to show A_{XAC} , analyzed through various assays i.e., FRAP (EC_{50} 0.1398 mg/mL), ABTS (IC_{50} 0.0442 mg/mL), DPPH (IC_{50} 0.26 mg/mL) compared to the standard ascorbic acid (IC_{50} 0.0165 mg/mL) [6]. In addition, A_{XAC} of the BAR aqueous extract and silver nanoparticles (AgNPs) synthesized from the extract were evaluated using FRAP and DPPH assays. AgNPs exhibit higher activity than the extract [54].

Regional variations in BAR antioxidant activity highlight key methodological (e.g., solvent type, temperature, and duration) and biogeographic influences (soil composition, climate, and altitude).

Iranian ethanol extracts showed the highest radical scavenging activity (DPPH: 88.9 %, ABTS: 97.4 %), while Chinese aqueous extracts performed best in β -carotene bleaching (92.3 %), suggesting heat-stable components. Polish leaf extracts led in ORAC values (267.81 mg TE/g), indicating tissue-specific potency. However, inconsistent dosage units and extraction methods limit direct comparisons. Critical gaps remain in standardizing assays and isolating environmental effects. Future research should prioritize solvent optimization, controlled cultivation studies, and metabolomic profiling to clarify chemotypic differences. These steps would strengthen cross-study validity and applications.

4.2. Anticancer properties

As shown in Table 5, different parts of BAR have shown anticancer

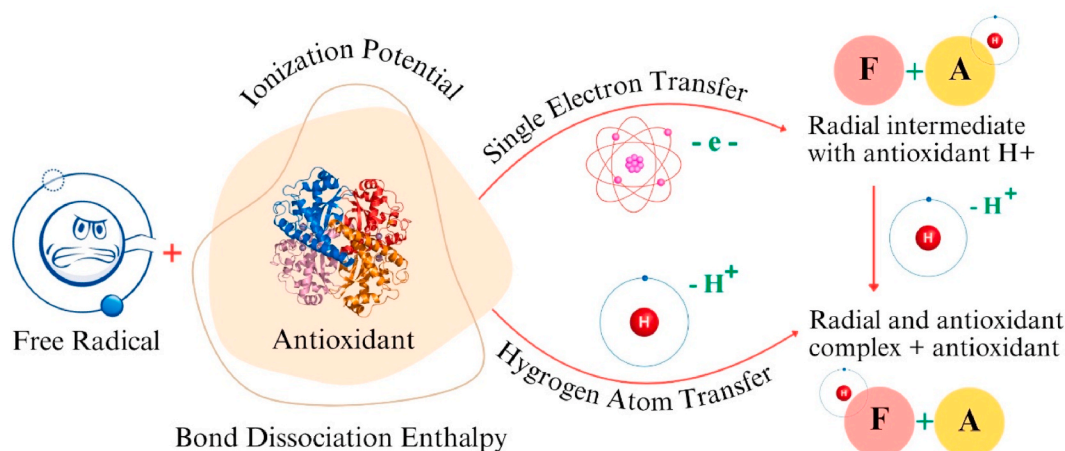


Fig. 1. Antioxidant mechanism of secondary metabolites.

activity. For example, BAR_F was evaluated for its chemopreventive activity induced by intraperitoneal injection of 200 mg/kg diethylnitrosamine (DEN), followed by acetylaminofluorene (0.02 % AAF) dissolved in corn oil in Sprague-Dawley rats. BAR_F (100 mg/kg) reduced enzyme activity, that is, gamma-glutamyl transferase (GGT), glutathione S-transferase (GST), and alkaline phosphatase (ALP), which was significantly lower than that of the control. AFP gene expression was not detected [55]. The aqueous extract of BAR_F showed anticancer effects in Sprague Dawley rats in the terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) assay, with a substantial increase in the number of apoptotic cells [56]. The ethanol extract of BAR root had IC_{50} values of 0.00454, 0.00384, and 0.00555 mg/mL against breast cancer cells (MCF), colon cancer cells (CACO), and liver cancer cells (HepG2), respectively, whereas berberine showed IC_{50} values of 0.00443, 0.01149, and 0.0051 mg/mL, respectively [57].

Aqueous and ethanol BAR_F extracts were reported to exhibit anticancer activity with IC_{50} values of 1 and 0.5 mg/mL after 72 h incubation, respectively against MCF-7 cell line. Although both extracts significantly inhibited MCF-7 cell proliferation, these changes were not observed in normal human breast epithelial cells (MCF10-A). The alcoholic extract was more effective at inducing apoptosis, as detected by DNA fragmentation in treated cancer cells [37]. In another study, the ethyl acetate extract of BAR root bark showed greater cytotoxicity (IC_{50} 3.54 μ g/mL) than the ethanol extract (IC_{50} = 597 μ g/mL) against the MCF-7 cell line; however, no cytotoxicity was observed against the normal cell line. Moreover, berberine had a similar effect on MCF-7 tumor cells as the ethanol extract, with non-significant differences, suggesting that the cytotoxicity of the ethanol extract may be primarily associated with berberine [52].

Ivan et al. [6] studied the anticancer effect of BAR hydro-ethanol stem bark extract at 6.25–400 μ g/mL, with no cytotoxicity against HUVEC (normal endothelial cells) and HT-29 (colon cancer cell lines), moderate cytotoxicity against HepG2 (hepatocellular cancer) and SK-OV-3 (human ovarian cancer) (IC_{50} > 100 μ g/mL after 48 h exposure), and excellent cytotoxicity against MDA-MB-231 (breast cancer cells), PE/CA-PJ49 (tongue cancer cells), and LoVo (colon cancer cells) with an IC_{50} > 50 μ g/mL after 48 h exposure. Another study examined the cytotoxicity of BAR root methanol extract (30, 3, 0.3, 0.03, and 0.003 μ g/mL), cisplatin, and the combined extract and drug. Human cervical cancer cells (HeLa) were found to be less sensitive to the individual root extract and cisplatin but showed an excellent synergistic effect [61]. A similar examination was carried out using BAR root methanol extract (30, 3, 0.3, 0.03, and 0.003 μ g/mL), ifosfamide, and a combination of the extract and drug. At 30 μ g/mL, HeLa cells were found to be less sensitive to the individual root extract (61 % cell viability) and ifosfamide (46.4 % cell viability) but showed an excellent

synergistic effect that is, 31.4 % cell viability [62].

The ethanol extract of BAR_F had greater anticancer activity against MCF-7 cells than doxorubicin [58]. BAR_F ethanol extract has been reported to show antineoplastic activity against MCF-7 cells by increasing the mRNA levels of p53 and Bax and decreasing Bcl-2. This activity is attributed to chlorogenic acid, a phenolic phytochemical [59]. A previous study indicated that BAR_F acetone extract induced apoptosis in MCF-7 cells, as assessed by the 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay [60]. It was stated that BAR root methanolic extract is more sensitive to colon cancer cells than control cells with an IC_{50} = 4.3, and 46.1 μ g/mL for LS180 and HT-29 cells, respectively, while it possessed an IC_{50} = 50.2 μ g/mL against control colon epithelial CCD841 CoN cells [63]. Ciorîță et al. [16] reported that BAR fresh stem bark ethanol extract exhibited anticancer potential against the human skin melanoma cell line (A375) and the lung adenocarcinoma cell line (A549), with an IC_{50} = 0.04 % for both cell lines, as assessed by the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Pluronic F-127 nanoparticles encapsulated with Fe_2O_3 from BAR leaf aqueous extract were analyzed for anticancer activity against breast cancer cells using the MTT assay. These findings indicate that MCF-7 cells are more sensitive to PF-127 Fe_2O_3 NPs than MDA-MB-231 [64]. AgNPs synthesized from BAR leaf aqueous extract were reported to possess anticancer activity against MCF-7 cells with an IC_{50} of 20.2 μ g/mL at 48 h, as assessed by the MTT assay [65].

Regional variability in the cytotoxic potency of BAR extracts was evident in comparative studies. Egyptian root ethanol extracts demonstrated the highest activity, with IC_{50} values of 0.004–0.0055 mg/mL against MCF-7 and LS180 cell lines. Moroccan and Polish samples exhibited lower but still significant potency, with IC_{50} values in the low micromolar range. In contrast, Iranian fruit extracts required higher concentrations (IC_{50} ~1.0 mg/mL), though their ethanol fractions upregulated pro-apoptotic genes (p53, Bax). Romanian extracts showed weaker effects (IC_{50} > 100 μ g/mL), while Saudi and Iranian nanoparticle formulations (e.g., AgNPs) markedly enhanced cytotoxicity (IC_{50} ~20 μ g/mL at 48 h). These variations likely stem from plant part selection, extraction solvents, and assay systems. Overall, ethanol and nanocarrier systems consistently yielded better activity. However, dose discrepancies and lack of apoptosis validation markers in some studies call for standardized protocols and mechanistic exploration in future research.

4.3. Other health-promoting properties

The antiulcer, antipulmonary, and anti-inflammatory properties of BAR are summarized in Table 6. Prolonged inflammation triggers

Table 4
Antioxidant activity of different parts of *B. vulgaris*.

Origin	Plant part	Extraction solvent	Dosage	Assay	Results	Standard drug	References
Iran	Fruit	Water	5 mg/mL	DPPH	74.71 %	Ascorbic Acid	[37]
			2.5 g/l	FRAP	397.68 M Fe(II)/g DW	–	
		Ethanol	5 mg/mL	DPPH	88.9 %	Ascorbic Acid	[51]
			2.5 g/l	FRAP	542.93 M Fe(II)/g DW	–	
		Methanol	–	DPPH	60.23 %	–	[38]
		–	–	FRAP	60.29 TE mmol/L	–	
		–	–	Fe ²⁺ chelating	31.44 %	–	[38]
		Acetone	2 mg/mL	DPPH	68.40 %	BHT i.e., 78.65 %	
		Ethanol	–	–	40.75 %	–	[5]
		Water	–	–	45.45 %	–	
Turkey	Fruit infusion	Water	2 mg/mL	ABTS	60.20 %	–	[25]
					97.61 %	BHT i.e., 98.65 %	
	Fruit decoction	Ethanol	2 mg/mL	ABTS	97.44 %	–	[14]
					95.36 %	–	
	Fruit infusion	Water	20 µL	FRAP	96.54 %	–	[5]
					126.27 %	–	
	Fruit Decoction	Methanol	20 µL	ABTS	8.731 µmol TE/g	Trolox	[25]
					44.3 %	Ascorbic Acid	
	Leaf	Ethanol	–	DPPH	86.5 %	–	[40]
					21.4 %	–	
Saudi Arabia	Roots	Ethanol	–	DPPH	76.5 %	–	[41]
					40.44 %	–	
					83.53 %	–	
					34.38 %	–	
					76.28 %	–	
	Fruit	Methanol	–	DPPH	56.84 %	–	[24]
					92.34 %	–	
					IC ₅₀ 88.0 µg/mL	–	
					SC ₅₀ 0.10 mg/mL	–	
					621.02 µmol/g	–	
Moroccan	Root barks	Ethanol	–	DPPH	IC ₅₀ 69.65 µg/mL	–	[52]
					IC ₅₀ 77.75 µg/mL	–	
					70.2 % RSA	–	
					93.0 % RSA	–	
					64.73 mg TE/g	–	
	Fruit	Ethanol	0.5 mg/mL	DPPH	65.25 mg TE/g	–	[43]
					63.88 mg TE/g	–	
					117.93 mg TE/g	–	
					140.49 mg TE/g	–	
					122.96 mg TE/g	–	
Russia	Fruit	Ethanol	0.5 mg/mL	DPPH	215.25 mg TE/g	–	[6]
					267.81 mg TE/g	–	
					167.70 mg TE/g	–	
					EC ₅₀ 0.1398 mg/mL	–	
					IC ₅₀ 0.0442 mg/mL	–	
	Stem bark	50 % ethanol	–	DPPH	IC ₅₀ 0.2610 mg/mL	–	[54]
					14.28 mM/mL	–	
					15.86 mM/mL	–	
					85.64 %	–	
					90.24 %	–	

ABTS: 2,2-azino-bis-3-ethylbenzothiazoline-6-sulphonic acid, AgNPs: silver nanoparticles synthesized from *B. vulgaris* fruit aqueous extract; BHA: butylated hydroxytoluene; DPPH: 2,2-diphenyl-1-picrylhydrazyl; DW: dry weight; FRAP: ferric reducing power assay; TE: Trolox equivalent; TBA: thiobarbituric acid.

immune cells to overproduce free radicals, damaging tissues and contributing to disease. Carcinogenic stimuli disrupt the epithelium, prompting cytokine release and attracting neutrophils, worsening inflammation. Chronic inflammation leads to DNA damage, uncontrolled cell growth, and eventual tumour formation. Angiogenesis fuels this process by supplying oxygen and nutrients to proliferating abnormal cells (Fig. 2).

BAR phytochemical contents believed to counteract this systematically, as an example, BAR hydro-alcohol extract (2000 mg/mL) had anti-ulcerative effect by decrease in MDA (malondialdehyde) activity from 3.2 to 1.6 µmol/g similar to asacol in acetic acid induced inflammation in rats [66]. The aqueous extract of BAR_F was found to possess anticolitic effects against acetic acid-induced colitis in male Wistar rats. At higher doses of 750 and 1500 mg/kg, the BAR extract efficiently reduced the damage score, ulcer area, and ulcer index on a macroscale. However, its efficacy was inferior to that of the reference berberine alkaloid and hydrocortisone acetate enemas. Anthocyanins are responsible for this activity [67]. The aqueous extract of BAR seeds (900 mg/kg) was

reported to possess 74.81 % gastric protection, identical to omeprazole (75.52 %) against aspirin-induced gastric toxicity in male adult albino mice [68]. BAR seed powder was reported to exert gastroprotective effects by reducing tissue proliferation, infiltration of cells, and sloughing induced by aspirin. The maximum dose (900 mg/kg) exhibited similar results as the synthetic drug omeprazole [69]. Kapitonova et al. [70] investigated the gastroprotective properties of alcoholic leaf extract at a dose of 50 mg/kg against ethanol-induced gastric mucosal injury. The results revealed that it considerably increased the concentration of prostaglandin E₂ (84 ng/mL) compared to atropine and significantly reduced ulcer ratings. These effects are attributed to the flavonoids and tannins that constitute their polyphenolic complexes, which are responsible for their medicinal properties.

BAR_F hydroalcoholic extract significantly decreased the levels of MDA, hydroxyproline, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and transforming growth factor beta 1 (TGF-β1) in response to paraquat, that is, plant herbicide-induced pulmonary fibrosis in male rats. Evaluation of the chemical composition and immunological

Table 5
Anticancer activity of different parts of *B. vulgaris*.

Origin	Plant part	Extraction solvent	Animal/cell line	Drug/assay	Results	References
<i>In vivo</i> Iran	Fruit	–	Sprague dawley rats	i.p. DEN (200 mg/kg) followed by AAF (0.02 % in corn oil) TUNEL	100 mg/kg reduced enzymes activity i.e., GGT, GST and ALP significantly lower than control; $p < 0.05$	[55]
Iran <i>In vitro</i> Egypt	Root	Water	MCF, CACO, HepG2	–	Significant increase in apoptotic cells; $p < 0.05$	[56]
	Berberine	Ethanol			IC ₅₀ = 0.00454, 0.00384, and 0.00555 mg/mL; $p < 0.05$	[57]
					IC ₅₀ = 0.00443, 0.01149, and 0.0051 mg/mL; $p < 0.05$	
Iran	Fruit	Ethanol	MCF-7	–	IC ₅₀ 1.0 mg/mL after 72 h incubation; $p < 0.05$	[37]
		Water			IC ₅₀ 0.5	
		Ethanol	MCF-7	–	9 and 12 mg/mL had better activity than doxorubicin	[58]
					Increased the mRNA level of p53, Bax and decreased Bcl-2	[59]
Turkey		Acetone	MCF-7	XTT	Induced apoptosis	[60]
Moroccan	Root bark	Ethanol	MCF-7	MTT	IC ₅₀ 3.54 µg/mL	[52]
		Ethyl acetate			IC ₅₀ 596.71 µg/mL	
Romania	Stem bark	50 % ethanol	HepG2 SK-OV-3 LoVo MDA-MB-231 PE/CA-PJ49	–	IC ₅₀ > 100 µg/mL after 48 h exposure; $p < 0.05$	[6]
					IC ₅₀ > 50; $p < 0.05$	
Pakistan	Root	Methanol	HeLa	MTT	30 µg/mL showed 67 % cell viability	[61]
Pakistan			HeLa		30 µg/mL showed 61 % cell viability	[62]
Poland			LS180		IC ₅₀ 4.3 µg/mL; $p < 0.05$	[63]
			HT-29		IC ₅₀ 46.1 µg/mL; $p < 0.05$	
Romania	Stem bark	Ethanol	A375 and A549		IC ₅₀ 0.4 % for both cell lines	[16]
Saudi Arabia	PF127Fe ₂ O ₃ NPs from leaves	Water	MCF-7		IC ₅₀ 21.9, 44.18, and 51.58 µg/mL for 24, 48, and 72 h respectively; $p < 0.05$	[64]
			MDA-MB-231		IC ₅₀ 27.17, 45.64, and 75.96 µg/mL for 24, 48, and 72 h, respectively; $p < 0.05$	
Iran	AgNPs from leaf	Water	MCF-7		IC ₅₀ at 48 h was 20.27 µg/mL; $p < 0.05$	[65]

IC₅₀:50 % inhibitory level; MCF: breast cancer cells; CACO: colon cancer cells; HepG2: human liver cancer cells; i.p.: intraperitoneal (route of administration), DEN: diethylnitrosamine, AAF: acetylaminofluorene, SK-OV-3: human ovarian cancer cell, LoVo: colon cancer cell, MDA-MB-231: breast cancer cell, PE/CA-PJ49: tongue cancer cell, HeLa: human cervical cancer, 3T3: normal cell, PF127Fe₂O₃NPs: Pluronic F-127 NPs encapsulated with Fe₂O₃ from *B. vulgaris* leaf extract, AgNPs: silver NPs from leaves, LS180, and HT-29: human colon adenocarcinoma cell line, A375: human skin melanoma cell line, A549: lung adenocarcinoma cell line: MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay.

properties showed that their activity was mainly due to the alkaloid constituents [71]. Inflammation represents a protective physiological response that is commonly triggered by microbial invasion or tissue injury, including cell death, aiming to eliminate harmful stimuli and initiate repair processes [76]. Inflammation is an alteration in the normal functioning of vascular tissues that is caused by any type of injury or infection. It can be further divided into acute and chronic inflammation, which include the immune system, vascular system, and different cells in the damaged tissues [77].

Another study investigated the anti-inflammatory activities of total ethanolic extract (TEE), three alkaloid fractions, berberine, and oxyacanthine, from BAR roots. Their impact on *in vivo* (zymosan- and carrageenan-induced paw edema) and *in vitro* (acetic acid-induced vascular permeability and adjuvant-induced arthritis) complement activities was assessed. TEE has been proven to be the most effective against acute (carrageenan- and zymosan-induced paw edema) and chronic inflammation (an adjuvant arthritis model) [72]. The hydroalcoholic extract of BAR root demonstrated significant antinociceptive (pain-blocking) and anti-inflammatory effects in both acute and chronic phases of pain. The effective doses tested were 20, 40, 80, and 160 mg/kg. The reduction in the extract's effect after the administration of naloxone (an opioid receptor blocker) suggests that its mechanism of action is mediated through the opioid receptor pathway. This indicates the extract's potential for pain relief operates similarly to opioid drugs [73]. The anti-inflammatory effect of BAR_F aqueous extract was examined in a model of atherosclerosis-induced rabbit, reduced inflammatory mediators such as IL-6 and TNF-α in acute inflammation, and reduced macrophages per intimal area presenting chronic inflammation [74].

Another study investigated the anti-inflammatory effects of an alcoholic extract of BAR_F in rats. Doses of 150 and 300 mg/kg significantly reduced acute inflammation induced by formalin and acetic acid. The 300 mg/kg dose also significantly reduced chronic inflammation caused by a cotton implant. Furthermore, the extract demonstrated a significant analgesic effect by reducing the late phase of chronic pain [75].

Regional studies demonstrate BAR variable bioactivity, with Iranian ethanol fruit extracts matching Asacol's antiulcer effects and Pakistani seeds showing omeprazole comparable (74.8 %) gastric protection. Russian ethanol leaves surpassed atropine in ulcer reduction, while Bulgarian berberine outperformed crude extracts in arthritis models. Water-based Iranian/Bulgarian fruit extracts lowered TNF-α/IL-6 in cardiopulmonary studies. Ethanol extracts generally showed stronger anti-inflammatory effects, though model heterogeneity (Zymosan/carrageenan/atherosclerosis) and dose disparities hinder cross-study comparison. While therapeutic potential is evident, standardized extractions, dose-response studies, and mechanistic validation remain critical for clinical translation.

4.4. Antimicrobial activity

In 1928, antibiotics entered their golden age after the discovery of penicillin; antibiotics may be artificially synthesized or extracted from natural products. The long-term use of antibiotics has led to the development of antibiotic resistance in bacteria, which is why microbial infection is the leading cause of morbidity and mortality. Currently, people are interested in natural antimicrobial agents, particularly those extracted from plants. Different parts of BAR showed excellent

Table 6
Antiulcer, anti-pulmonary and anti-inflammatory properties of *B. vulgaris*.

Origin	Plant part	Extraction solvent	Animal model	Drug	Dose	Results	Reference
Iran	Fruit	Aqueous ethanol	Rats	Asacol	2000 mg/mL	Decreased MDA activity from 3.2 to 1.6 $\mu\text{mol/g}$ similar to asacol; $p < 0.05$	[66]
Iran			Male Wistar rats	Hydrocortisone acetate and prednisolone	750, 1500 mg/kg	Effectively diminished damage score, ulcer area and ulcer index macroscopically; $p < 0.05$	[67]
Pakistan	Seed	Distilled water	Male adult albino mice	Aspirin	900 mg/kg	Showed 74.81 % gastric protection identical to omeprazole (75.52 %); $p < 0.05$	[68]
Pakistan	Seed					Exhibited similar results to the omeprazole; $p < 0.05$	[69]
Russia	Leaf	Ethanol	Sprague-Dawley rats	Atropine	50 mg/kg	Reduced the macroscopic ulcer score and lesion index more than atropine $p < 0.05$	[70]
Iran	Fruit	Aqueous Ethanol	Male rats	Paraquat	200 and 400 mg/kg/d	Significantly decrease the level of MDA, hydroxyproline, TNF- α , IL-6 and TGF- β 1; $p < 0.05$	[71]
Bulgaria	Root extract	Ethanol	<i>In vitro</i>	Acetic acid induced vascular permeability	10 mg/kg	30 % inhibition	[72]
	Berberine from roots				2 mg/kg	57 % inhibition	
	Root extract			Adjuvant-induced arthritis	20 mg/kg/d	14 % reduction in edema volume observed on the 28th day	
	Berberine from roots				2 mg/kg/d	20 % reduction in edema volume observed on the 28th day	
	Root		Male mice	Zymosan	20–200	Dose-dependent inhibitory effect (35–68 %)	
	Fruit	Water	Rabbit	Carrageenan	100 and 200	Decreased edema volume 10.4 % and 23.6 %	
				Atherosclerosis	50 mg/kg	Reduced inflammatory mediators i.e., IL-6 and TNF- α	[73]

AP, alkaline phosphatase; BVFE, *Berberis vulgaris* fruit extract; IL-6: Interleukin-6, TGF- β 1: Transforming Growth Factor Beta 1; TNF- α : Tumor Necrosis Factor-alpha, MDA, malondialdehyde; ZOI, zone of inhibition.

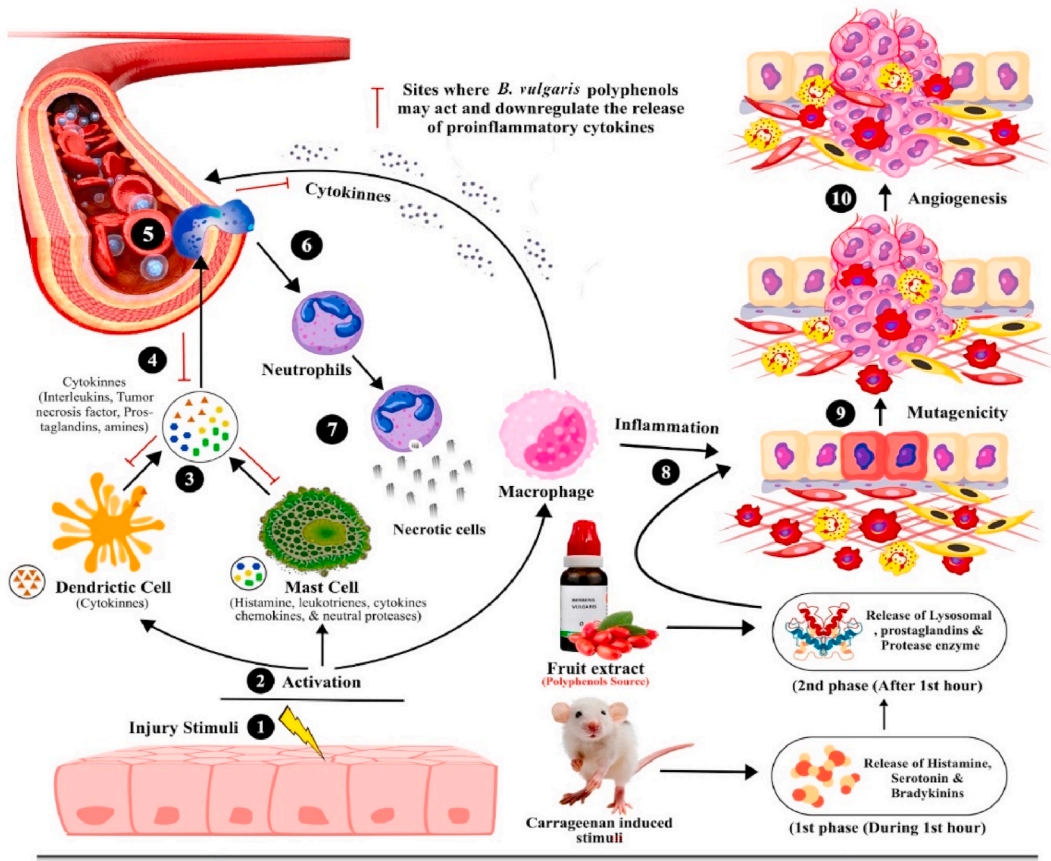


Fig. 2. Anti-inflammatory mechanism of polyphenols. Sourced and modified from our previous article (Saeed et al., 2024).

Table 7
Antimicrobial activity of different parts of *B. vulgaris*.

	Plant part	Extraction solvent	Target strain	Results	References
Antibacterial Activity					
Iran	Stem $p < 0.05$	Ethanol	<i>Streptococcus sobrinus</i>	ZOI 14 mm;	[4]
			<i>S. sanguinis</i>	9.0; $p < 0.05$	
			<i>S. salivaris</i>	11.3; $p < 0.05$	
			<i>S. mutans</i>	7.6; $p < 0.05$	
			<i>Lactobacill rhamnosus</i>	7.8; $p < 0.05$	
	Fruit $p < 0.05$		<i>Streptococcus sobrinus</i>	7.3; $p < 0.05$	
			<i>S. sanguinis</i>	7.6; $p < 0.05$	
			<i>S. salivaris</i>	10.0; $p < 0.05$	
			<i>S. mutans</i>	8.0; $p < 0.05$	
			<i>Lactobacill rhamnosus</i>	6.0; $p < 0.05$	
	Leaf		<i>Streptococcus sobrinus</i>	6.0	
			<i>S. sanguinis</i>	6.0	
			<i>S. salivaris</i>	9.3	
			<i>S. mutans</i>	6.3	
			<i>Lactobacill rhamnosus</i>	6.6	
Saudi Arabia	Root	Ethanol	<i>S. aureus</i>	ZOI 19 mm	[14]
			<i>E. coli</i> HB101	2.3	
			<i>S. enteritis</i>	1.5	
			<i>E. coli</i> Cip812	2.0	
	Leaf		<i>S. aureus</i>	1.75	
			<i>E. coli</i> HB101	1.95	
			<i>S. enteritis</i>	1.35	
			<i>E. coli</i> Cip812	1.7	
Iran	Fruit $p < 0.05$	Ethanol	<i>Aeromonas hydrophila</i>	MIC 100 µg/mL	[39]
			<i>Streptococcus iniae</i>	100	
			<i>Lactococcus garvieae</i>	100	
			<i>Yersinia ruckeri</i>	100	
			<i>Listeria monocytogens</i>	50	
			<i>E. coli</i>	50	
Turkey	Fruit	Distilled Water	<i>Bacillus cereus</i>	ZOI 1–7 mm	[40]
			<i>Salmonella typhimurium</i>	8–15	
			<i>Yersinia enterocolitica</i>	1–7	
			<i>S. aureus</i>	8–15	
Pakistan	Leaf	Methanol	<i>P. aeruginosa</i>	16	[76]
Turkey	Fruit	Ethanol	Gram Positive	MIC 32	[42]
			B1	mg/mL	
			B2	16	
			B3	16	
			B4	8	
			B5	32	
			B6	32	
			B7	32	
			B8	32	
			B9	32	
			B10	32	
			Gram negative	8	
			B11		
			B12	32	
			B15	32	
			B17	16	
			B18	32	

Table 7 (continued)

	Plant part	Extraction solvent	Target strain	Results	References
Slovakia	AgNPs	Water	<i>S. aureus</i>	88.55 % inhibition	[54]
	<i>p</i> < 0.05		<i>E. coli</i>	88.06 %	
Antifungal activity					
Saudi Arabia	Root	Ethanol	<i>A. flavus</i>	MIC 90 µg/ml	[14]
			<i>A. niger</i>	90	
			<i>A. parasiticus</i>	100	
			<i>A. ochraceous</i>	80	
			<i>A. carbonarius</i>	120	
			<i>F. proliferitum</i>	150	
			<i>P. verrucosum</i>	140	
	Leaf		<i>A. flavus</i>	70	
			<i>A. niger</i>	75	
			<i>A. parasiticus</i>	85	
			<i>A. ochraceous</i>	60	
			<i>A. carbonarius</i>	100	
			<i>F. proliferitum</i>	125	
			<i>P. verrucosum</i>	120	
			<i>M. gypseum</i>	4 mg/mL	
Pakistan	Leaf	Methanol	<i>Fusarium solani</i>	ZOI 10 mm	[76]
			<i>Alternaria alternate</i>	16	

ZOI, zone of inhibition; MIC, minimum inhibitory concentration; AgNPs, silver nanoparticles synthesized from aqueous barberry fruit extract.

antimicrobial activity, as shown in Table 7. For example, BAR_F and leaf and stem extracts have been tested against bacteria associated with caries. The stem, fruit, and leaf ethanolic extracts exhibited ZOI (zone of inhibition) against caries bacteria, such as *S. sobrinus* (14, 7.3, 6 mm), *S. sanguinis* (9, 7.6, 6 mm), *S. salivaris* (11.3, 10, 9.3 mm), *S. mutans* (7.6, 8, 6.3 mm), *Lactobacillus rhamnosus* (7.8, 6, 6.6 mm), respectively, similar to the standard drug chlorhexidine, which showed ZOI (18, 15, 16, 16, 17 mm) against the targeted strains [4]. Similarly, the antibacterial activity of BAR root and leaf ethanol extracts was evaluated using agar diffusion and microdilution broth production and showed effectiveness against all tested bacterial strains [14].

Dietary BAR_F ethanolic extract (150–750 mg/kg) significantly reduced activity of *Aeromonas hydrophila*, *Streptococcus iniae*, *Lactococcus garvieae*, *Yersinia ruckeri*, *Escherichia coli*, and *Listeria monocytogenes* compared with extract free diet in Siberian sturgeon [39]. Several years ago, the antibacterial activity of BAR was tested against important foodborne pathogenic bacteria. The aqueous extract inhibited the growth of the targeted bacterial strains, except *E. coli*. It showed zone of inhibition (ZOI) = 1–7 mm against *Bacillus cereus* and *Yersinia enterocolitica*, 8–15 mm against *Salmonella typhimurium* and *Staphylococcus aureus* [40]. BAR leaf methanolic extract was tested against single Gram-positive *S. aureus*, 6 g-negative bacteria (*E. coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumonia*, *Shigella dysenteriae* and three fungal pathogens (*Fusarium solani*, *Alternaria alternata*, *Candida albicans*) using the agar well diffusion method. The extract showed no remarkable action against all tested microbes except *P. aeruginosa* which showed good activity with 16 mm ZOI; for *C. albicans* ZOI was 21 mm [78]. Among the various species of *Berberis*, *B. vulgaris* L. generally exhibited a larger ZOI compared to the other samples, and zone diameters ranged from 18 to 39 mm against all gram-positive and gram-negative bacteria [42]. BAR_F methanol extract reported to show the highest inhibition against *Bacillus subtilis* (59.89 %) and *E. coli* (59.8 %) as compared to butanol and water extracts. Butanol extract was effective against *P. aeruginosa* (48.59 %) and *Xanthomonas campestris* (48.03 %). Followed by methanol extract. The aqueous extract showed the weakest activity, including no inhibition (0 %) against *Staphylococcus aureus*. Activity against all strains was dose-dependent [79].

The antibacterial effect of biogenic AgNPs (synthesized from the

aqueous extract of BAR_F) against pathogenic bacteria was also studied using the agar well diffusion method. AgNPs were slightly more effective against *S. aureus* (Gram-positive) than *E. coli* (Gram-negative), but the difference between the two strains was not significant. AgNPs showed antibacterial activity similar to that of the positive control gentamicin sulfate [54]. BAR root and leaf extracts were tested for antifungal activity, and both extracts inhibited mycelial growth of *Penicillium verrucosum*, *Fusarium proliferatum*, *Aspergillus ochraceus*, *Aspergillus niger*, and *Aspergillus flavus*. However, root extract exhibited the highest level of inhibition [14]. Likewise, in another investigation, *B. vulgaris* root extract exhibited notable activity against *Staphylococcus aureus* and *Streptococcus pyogenes*, supporting its traditional use for skin and throat infections. The antibacterial potency was directly linked to its alkaloid content, particularly berberine [80]. Like BAR_F nanoparticles, an increase in antibacterial activity was also observed when silver nanoparticles (AgNO₃) were successfully synthesized using *B. vulgaris* leaf and root extract. The spherical nanoparticles, sized 30–70 nm, were produced via a green, non-toxic method. These bio-synthesized nanoparticles demonstrated high antibacterial activity against *E. coli* and *S. aureus* [81].

The antifungal activities of *B. vulgaris* and *B. integerrima* methanolic fruit extracts against *Fusarium solani* and *Fusarium graminearum* were tested. Microdilution, growth area measurements, and morphological analysis were performed. A scanning electron microscope (SEM) was used to assess the changes. The BAR_F extract had MIC (minimum inhibitory concentration) values of 150 and 75 mg/mL for *F. graminearum* and *F. solani*. Scanning electron microscopy (SEM) showed that both medicinal herb extracts changed mycelial structure. Additionally, they inhibited conidial formation in a dose-dependent [82].

Antimicrobial activity of *B. vulgaris* varies by region, plant part, and solvent. Iranian ethanol stem/fruit extracts moderately inhibited oral

Streptococcus spp. (ZOI 7–14 mm), while Pakistani methanolic leaf extracts were more effective against *P. aeruginosa* and *Fusarium solani*. Saudi ethanol root extracts showed broad-spectrum activity, particularly against *S. aureus* (ZOI 19 mm) and toxigenic fungi (*A. flavus*, *F. proliferatum*; MIC 80–150 µg/mL). Turkish water/ethanol extracts had variable effects on foodborne pathogens, whereas Slovakian AgNPs (aqueous-derived) achieved >88 % bacterial inhibition, indicating enhanced delivery. Ethanol extracts and nanoparticles consistently outperformed other methods, but differences in microbial strains, solvents, and dosage metrics hinder direct comparisons. Future studies should standardize protocols and explore mechanistic synergy against resistant strains.

5. Clinical trials

Table 8 shows the clinical trials performed in Iran to evaluate the efficiency of different parts of the BAR against some diseases. For instance Ref. [17], studied the effect of BAR_F extract (3 g) on type 2 diabetes (T2D) patients for 3 months and found significant decreases in serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), apo B, glucose, and insulin, and a significant increase in total antioxidant capacity (TAC). Another study evaluated the effect of BAR_F extract on glycemic control in T2D patients. For this purpose, the extract (2 mg/day) was administered to 13 patients with T2D for 8 weeks. Patient's serum glucose and glycated hemoglobin (HbA1c) was reduced from 161 to 136 mg/dL and 8.10 to 7.07 mg/dL, respectively [83].

Cardiovascular disease (CVD) is strongly associated with metabolic syndromes. Heat shock proteins (HSPs) increase the risk of CVD. One study investigated the effect of BAR on HSP and high-sensitivity C-reactive protein (hs-CRP) antibody titers in 106 patients with metabolic syndrome. The patients were randomized to receive BAR (200 mg/day)

Table 8
Clinical trials of *B. vulgaris* in Iran.

Plant part	Disease	Extraction solvent	Dosage and duration	Study design and subjects	Outcomes	References
Fruit	Diabetes	Water	3 g/d for 3 months	DB, RCT 31	Decreased blood glucose level from 140.2 to 117 mg/d	[17]
Fruit powder		–	1 mg for 8 weeks	DB, RCT 30	Reduced serum glucose 161.31–136.15 mg/dL and HbA1c levels to 8.10–7.07 mg/dL; $p < 0.05$	[83]
	Metabolic syndrome	–	200 mg/d for 6 weeks	DB, RCT 106	Improved lipid profile and reduced significantly anti-HSPs 27 and 60 and hs-CRP; $p < 0.05$	[84]
		–	200 mg/d for 6 weeks	DB, RCT106	Reduced pro-oxidant–antioxidant balance up to 80 AU; $p = 0.32$	[85]
Processed fruit		–	10 mL/d for 8 weeks	DB, RCT 57	Decrease in LDL, increased HDL, and insulin concentration; $p = 0.04$	[86]
Leaves	Bacterial vaginosis	Ethanol	Vaginal gel containing 5 % <i>B. vulgaris</i>	DB, RCT 175	Showed 10 % recovery rate while Metronidazole alone showed 42.5 %; $p < 0.05$	[86]
Root and barks	Dental	Alkaloids		DB, RCT 105	Reduced 56 % plaque index and 33.55 % gingival index	[88]
Root	Metabolic syndrome	Extract	500 mg/d for 3 months	Three-blind RCT	The metabolic syndrome aggravated, weight and waist size also increased	[89]
Fruit powder	Diabetes	–	1000 mg/d for 8 weeks	DB clinical trial	Significantly reduced BMI, WHR, FBs, TG, LDL-c and TC/HDL-C, changed visfatin was too; $p = 0.01$	[90]
Fruit	Metabolic syndrome	Water	550 mg/d tablet daily for 3 weeks	DB RCT	Reduced significantly serum cholesterol, systolic blood pressure, waist circumference and hematocrit; $p = 0.02$	[91]
Fruit powder	Hypertension	–	10 g/d for 8 weeks	Single-blind RCT	Improved the FMD and decreased the plasma ICAM-1, lowered MCP-1; $p = 0.33$	[15]
Root	Opiate withdrawal syndrome	Extract capsules	500 mg twice for 4 weeks	DB clinical trial	Improved symptoms of opiate withdrawal syndrome significantly	[92]
Fruit	Diabetes	Extract		DB randomized clinical trial	Decreased significantly serum TG, TC, LDL-c, apo B ($p = 0.01$) glucose, and insulin, and increased in TAC ($p = 0.02$)	[17]
Fruit	Acne vulgaris	Juice	100 mL daily for 30 days	A Placebo-Controlled Study	Significantly reduced inflamed ($p = 0.01$) and total acne lesions ($p = 0.02$) but had no effect on noninflamed lesions ($p = 0.33$)	[93]

FMD: flow-mediated dilation, ICAM-1: intracellular adhesion molecule-1, MCP-1: macrophage/monocyte chemo-attractant protein-1, BMI: body mass index, WHR: waist to height ratio, FBs: fasting blood sugar, TG: triglycerides, TC: total cholesterol, LDL-c: low-density lipoprotein cholesterol, HDL-c: high-density lipoprotein cholesterol, HSP: heat shock protein, hs-CRP: high sensitivity C-reactive protein, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, RCT: Randomized clinical trial, DB: Double blind.

or placebo capsules for six weeks. It reduced anti-HSP (anti-heat shock protein) 27 and 60, hs-CRP, low-density lipoprotein, and TC while increasing high-density cholesterol. These findings suggest that BAR supplementation may improve cardiovascular health markers in these patients [84]. Similarly, a study explored how antioxidant-rich BAR_F affects the pro-oxidant-antioxidant balance (PAB) of patients with metabolic syndrome. A total of 106 patients received BAR or placebo capsules for six weeks. The initial PAB readings were similar between groups. BAR significantly decreased PAB ($P = 0.022$) but not in the control group. BAR supplementation reduced oxidative stress in these individuals more than PAB supplementation ($P = 0.01$) [85]. A randomized controlled clinical experiment with 57 T2D patients were divided into three groups: BAR ($n = 19$), apple vinegar ($n = 19$), and control ($n = 19$) examined the effects of processed BAR on metabolic syndrome components. Body measurements included height, weight, cholesterol, TG, glucose, and insulin levels at baseline and week 8. The BAR group showed substantial decreases in low density lipoprotein-cholesterol (LDL-C) and total/high density lipoprotein-cholesterol (HDL-C) ratio, and an increase in HDL-cholesterol ($P < 0.05$), but no changes in body mass index (BMI), TC, TG, or glucose. Insulin resistance and insulin levels were increased in all groups ($P < 0.001$). The study concluded that processed BAR improved certain risk factors for atherosclerosis [86].

Moreover, in 120 women, BAR 5 % and *Myrtus communis* L 2 % vaginal gels in a metronidazole base were compared with metronidazole gel alone for bacterial vaginosis treatment. The study found that the herbal gels outperformed metronidazole alone ($p < 0.001$), with no significant difference between the two treatments ($P = 0.18$). The herbal gel group had no relapse, but the 30 % metronidazole group did. *Myrtus communis* L. or BAR added to metronidazole enhanced bacterial vaginosis treatment [87].

Similarly, dental cleaning and plaque reduction using herbal extracts have been successful. A dental gel with BAR extract was tested for gingivitis and plaque management. A double-blind clinical experiment divided 45 boys aged 11-12-year, into the BAR gel, placebo gel, and Colgate antiplaque toothpaste groups. The BAR gel reduced plaque index (PI) by 56 % after 21 days compared to 18.5 % for the placebo and 44 % for Colgate. Significant differences have been reported between BAR and placebo and placebo and Colgate groups, but not between BAR and Colgate [83].

In another three-blind randomized trial, patients with schizophrenia received either BAR root extract or a placebo for three months. Initial measurements showed no significant differences between the groups, but post-treatment results showed that metabolic syndrome worsened in both groups, with an increase in weight and waist size [86]. Additionally, BAR is anti-diabetic and anti-atherogenic. Over eight weeks, this double-blind trial examined the effects of BAR on visfatin and metabolic profiles in 40 T2D mellitus patients. Patients were randomly assigned to receive 1000 mg BAR daily or a placebo. The TC, TG, HDL-C, LDL-C, and visfatin levels in the BAR group improved significantly compared to those in the placebo group. The study found that BAR improved T2DM patients' lipid profiles and visfatin levels [85].

The treatment of metabolic syndrome using BAR has also been explored. A randomized, placebo-controlled, double-blind trial provided 60 patients with BAR or placebo tablets daily for three weeks. Before and after treatment, TC, LDL, HDL, TG, FBS, and hematocrit were assessed. The BAR group had a lower systolic blood pressure, waist circumference, and hematocrit. BAR also dramatically lowered serum cholesterol levels compared to placebo [86]. In an eight-week randomized controlled experiment [15], hypertensive participants took 10 g/day of dried BAR or placebo. Before and after the intervention, BAR significantly enhanced brachial flow-mediated dilation (FMD) and lowered plasma intercellular adhesion molecule 1 (ICAM-1) and monocyte chemo-attractant protein-1 (MCP-1) levels compared with placebo. In hypertensive patients, BAR consumption improves vascular function and inflammation [15]. The effects of BAR extract on opiate withdrawal

syndrome, depression, anxiety, stress, and sleep quality in methadone maintenance therapy opioid addicts. Fifty-two addicts received 500 mg BAR extract capsules or placebo twice daily for four weeks. The participants were assessed at baseline and after 7, 14, and 28 days using the clinical Opiate Withdrawal Scale (COWS), Pittsburgh Sleep Quality Inventory (PSQI) and Depression Anxiety Stress Scales-21 (DASS-21). BAR significantly improved opiate withdrawal symptoms, but not sadness, anxiety, stress, or sleep quality, compared to placebo [87].

Clinical trials in Iran demonstrate BAR therapeutic potential for diabetes, metabolic syndrome, hypertension, and acne. Both aqueous and ethanol fruit extracts/powders significantly improved glycemic control (reduced fasting glucose, HbA1c), lipid profiles, and inflammatory markers. Notably, one metabolic syndrome study reported adverse effects with root extract, emphasizing part-dependent bioactivity. While vaginal gel and dental applications showed partial efficacy, they underperformed compared to conventional therapies.

Importantly, all the formulations of *B. vulgaris* (fruit powder, aqueous extracts, and alkaloid-rich formulations) were generally well tolerated and no serious adverse impacts were reported across studies involving diabetic, hypertensive, and metabolic syndrome patients. However, considerable variability in dosage and preparation forms (ranging from 200 mg to 10 g/day, or 100 mL juice to 550 mg tablets) complicates the interpretation of optimal therapeutic levels. Although short-term trials (4–12 weeks) indicate favorable safety outcomes, long-term safety data are lacking. These findings emphasize the need for standardized formulations and long-term safety assessments to establish consistent clinical use.

6. Conclusion

BAR has gained recognition as a versatile nutraceutical and therapeutic agent, connecting traditional herbal medicine with modern pharmacological applications. Its diverse phytochemical composition, particularly berberine and polyphenols has demonstrated effectiveness in addressing metabolic disorders, inflammatory conditions, and infectious diseases, supported by laboratory, animal, and early clinical studies. Despite these promising findings, challenges remain in standardization, understanding precise mechanisms of action, and ensuring sustainable cultivation practices.

To advance research and application, several key steps should be taken. First, methodological consistency must be established, including standardized protocols for extraction, dosing, and bioactivity testing, such as oxygen radical absorbance capacity (ORAC) for antioxidants and minimum inhibitory concentration (MIC) for antimicrobial effects. Clinically, large-scale, long-term trials, preferably registered through platforms like [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT) should be prioritized, particularly for diabetes and cardiovascular disease, with thorough safety evaluations. Additionally, innovative approaches such as nano-delivery systems and combination therapies could enhance bioavailability and efficacy. Finally, ecological sustainability must be addressed through responsible harvesting practices and *in vitro* propagation techniques to protect wild populations and maintain genetic diversity. These steps will help bridge existing gaps and maximize the plant's therapeutic potential.

CRedit authorship contribution statement

Muhammad Usama: Writing – review & editing, Writing – original draft. **Saeed Akhtar:** Writing – review & editing, Conceptualization. **Muhammad Qamar:** Writing – review & editing, Conceptualization. **Tariq Ismail:** Writing – review & editing, Conceptualization. **Wisha Saeed:** Writing – review & editing, Methodology. **Muhammad Zulqarnain Khan:** Writing – review & editing, Methodology. **Elham Assadpour:** Writing – review & editing. **Seid Mahdi Jafari:** Writing – review & editing. **Tuba Esatbeyoglu:** Writing – review & editing, Funding acquisition.

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Declaration of competing interest

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Data availability

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

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