

**PUNICA GRANATUM FLOWER AND HIBISCUS SABDARIFFA CALYX: A NARRATIVE REVIEW OF PHYTOCHEMISTRY, ANTIOXIDANT MECHANISMS, AND SYNERGISTIC POTENTIAL IN OXIDATIVE STRESS MANAGEMENT**

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**ABSTRACT**

Oxidative stress, resulting from an imbalance between free radical production and antioxidant defense mechanisms, underlies the pathogenesis of numerous chronic diseases including cardiovascular disorders, cancer, diabetes, and neurodegenerative conditions. The global burden of these diseases continues to rise, with cardiovascular diseases alone causing 19.2 million deaths annually. In Yemen, non-communicable diseases account for 42% of total deaths, with substantial underdiagnosis of conditions like type 2 diabetes highlighting urgent needs for accessible preventive interventions. This narrative review synthesizes the literature on two medicinal plants with significant antioxidant potential: *Punica granatum* (pomegranate) flower and *Hibiscus sabdariffa* (roselle) calyx. Both species are cultivated in Yemen and hold prominent positions in traditional medicine. Pomegranate flowers are rich in ellagitannins, particularly punicalagin, which constitute the predominant phytochemical class and are metabolized by gut microbiota to urolithins with enhanced bioavailability.<sup>[1-5]</sup> *Hibiscus sabdariffa* calyces contain high concentrations of anthocyanins, primarily delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside, along with organic acids including hibiscus acid and phenolic compounds such as chlorogenic acid.<sup>[6-10]</sup> Both extracts demonstrate potent antioxidant activities through multiple mechanisms including direct reactive oxygen species scavenging, metal chelation, activation of the Nrf2 signaling pathway, and upregulation of endogenous antioxidant enzymes.<sup>[11-15]</sup> Their complementary phytochemical profiles and mechanisms of action provide a strong scientific rationale for polyherbal combinations targeting oxidative stress-related disorders. This review consolidates evidence supporting the traditional uses, phytochemistry, and pharmacological properties of these two Yemeni medicinal plants.

**KEYWORDS:** *Punica granatum*, pomegranate flower, *Hibiscus sabdariffa*, roselle, antioxidant, oxidative stress, Nrf2 pathway, polyphenols, ellagitannins, anthocyanins, Yemeni traditional medicine.

**1. INTRODUCTION**

Free radicals are unstable molecular species with unpaired electrons that initiate cellular damage through oxidative reactions.<sup>[16]</sup> These reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated from both endogenous metabolism, particularly during

mitochondrial oxidative phosphorylation, and exogenous sources including cigarette smoke, air pollution, and ultraviolet radiation.<sup>[17]</sup> Oxidative stress occurs when free radical production overwhelms antioxidant defense mechanisms, resulting in damage to lipids, proteins, and DNA.<sup>[18]</sup> This imbalance contributes to numerous

chronic diseases including cardiovascular disorders, cancer, diabetes, and neurodegenerative conditions through mechanisms involving lipid peroxidation, protein oxidation, and genomic instability.<sup>[19]</sup>

The global burden of oxidative stress-related diseases is substantial and increasing. Cardiovascular diseases caused 19.2 million deaths globally in 2023, representing the leading cause of mortality worldwide.<sup>[20]</sup> The global disability-adjusted life years from cardiovascular disease increased from 320 million in 1990 to 437 million in 2023, demonstrating a 1.4-fold rise over three decades. Ischemic heart disease remains the primary cause of cardiovascular mortality with an age-standardized rate of 108.8 deaths per 100,000 people globally.<sup>[20]</sup>

In Yemen, non-communicable diseases accounted for 42 percent of total deaths in 2021, with all-ages non-communicable disease-related deaths increasing by 101.6 percent between 1990 and 2021.<sup>[21,22]</sup> The prevalence of type 2 diabetes mellitus in Yemen includes 366,000 diagnosed cases with an estimated 447,000 additional undiagnosed cases, indicating significant disease underdetection.<sup>[23]</sup> Among diabetic patients, hypertension affects 36.9 percent and obesity is present in 23.06 percent.<sup>[24]</sup>

Synthetic antioxidants including butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tert-butylhydroquinone (TBHQ) have demonstrated potential hepatotoxicity, nephrotoxicity, and carcinogenic effects, necessitating exploration of natural alternatives.<sup>[25,26]</sup> Plant-based antioxidants offer safer alternatives through multiple mechanisms including free radical scavenging, metal chelation, and modulation of endogenous antioxidant enzymes.<sup>[19]</sup>

Yemen possesses rich traditional herbal medicine knowledge transmitted orally across generations, belonging to ancient Arabic medical traditions with Greek and Indian influences.<sup>[27]</sup> Ethnobotanical surveys documented 195 medicinal plant species from 55 families used for treating 155 ailments in central Abyan governorate.<sup>[28]</sup> Approximately 60 percent of Yemeni medicinal plants appear in Ibn al-Baytar's classical *Materia Medica*, demonstrating historical continuity.<sup>[27]</sup>

This review focuses on two medicinal plants with significant antioxidant potential that are cultivated in Yemen: *Punica granatum* (pomegranate) flower and *Hibiscus sabdariffa* (roselle) calyx. Both species hold prominent positions in traditional Yemeni medicine and have been the subject of extensive phytochemical and pharmacological investigation. This narrative review aims to: (1) document their botanical characteristics and traditional uses in Yemen; (2) synthesize current knowledge of their phytochemical composition; (3) examine their antioxidant mechanisms of action; and (4) evaluate the scientific rationale for their combined use in polyherbal preparations targeting oxidative stress.

## 2. *Punica granatum* Flower (Pomegranate Flower)

### 2.1 Botanical Description

*Punica granatum* Linn., commonly known as pomegranate, belongs to the family Lythraceae and is characterized as a small multi-stemmed deciduous shrub or tree reaching heights of 5 to 10 meters with smooth dark grey bark and woody spiny stems.<sup>[29]</sup> The simple leaves are oblong or obovate, measuring 2 to 8 centimeters in length, arranged oppositely with shiny glabrous surfaces. Flowers appear solitary or in fascicles at branch apices, measuring 4 to 6 centimeters in diameter.<sup>[30]</sup> The hermaphroditic flowers consist of 5 to 7 wrinkled lanceolate petals that are brilliant orange-red in color, with a colored hypanthium possessing 5 to 8 lobes and a persistent calyx that remains attached to the mature fruit.<sup>[31]</sup>

### 2.2 Geographical Distribution and Cultivation in Yemen

Pomegranate cultivation in Yemen encompasses approximately 2,412 hectares with around 2,532,128 trees distributed across multiple governorates.<sup>[31]</sup> Saada accounts for 68 percent of total cultivated area, followed by Dhamar, Amran, Sana'a, and Taiz. Cultivation spans diverse agro-ecological zones from 21 meters above sea level in coastal Abyan to 2,300 meters in central highland regions between latitudes 13° and 17° North. Eight major local varieties are cultivated including Taefi, Orkobi, Mellies-Hada, Khazemy, Sommaty, Kodary, Chiny, and Mellies-Raudha, each adapted to specific regional conditions.<sup>[31]</sup>

### 2.3 Traditional Uses in Yemen for Health and Wellness

Pomegranate and its various plant parts have been utilized extensively in Yemeni traditional medicine for treating diverse health conditions, with practices rooted in ancient Arabic medical traditions.<sup>[27]</sup> The fruit peel and bark serve as traditional remedies for diarrhea, dysentery, and intestinal parasites due to their astringent and antimicrobial properties.<sup>[29]</sup> Pomegranate flowers are employed in traditional medicine for treating diarrhea and external injuries, while juice from flowers is used to stop nosebleeds.<sup>[32]</sup> The fresh root bark is prepared as an anthelmintic formulation, with the alkaloid punicine responsible for antiparasitic activity.<sup>[29]</sup> Ripe fruits are valued as laxatives and blood-enriching agents, considered beneficial for sore throat, sore eyes, brain diseases, and chest troubles.<sup>[29]</sup> In Persian and Islamic traditional medicine, pomegranate preparations have been prescribed for gastrointestinal disorders, respiratory problems, skin diseases, reproductive issues, and metabolic disorders.<sup>[33]</sup>

**Table 1: Traditional Medicinal Uses of Pomegranate Parts in Yemen and Regional Traditions.**

Plant Part	Traditional Medicinal Uses	Preparation Method	Therapeutic Indications
Flowers	Diarrhea treatment, nosebleeds, external injuries	Juice extract, dried powder	Gastrointestinal disorders, hemorrhage control, wound healing
Fruit Peel	Diarrhea, dysentery, intestinal parasites	Dried peel decoction	Antidiarrheal, antimicrobial, astringent
Root Bark	Anthelmintic (deworming)	Fresh bark extract	Intestinal parasite elimination
Ripe Fruit/Juice	Blood enrichment, laxative, throat/eye ailments	Fresh juice, fruit pulp	Cardiovascular tonic, vision support, respiratory health
Seeds	Heart, throat, eye tonic, digestive aid	Seed decoction, dried powder	Cardiac support, digestive strengthening
Bark	Purgative (strong laxative)	Bark extract	Severe constipation (with caution)

Source:<sup>[29,32,33,27]</sup>

## 2.4 Phytochemistry of *Punica granatum* Flower

### 2.4.1 Major Constituents

Pomegranate flowers contain a diverse array of bioactive phytochemicals dominated by polyphenolic compounds, with ellagitannins representing the most abundant and pharmacologically significant class.<sup>[1]</sup> Punicalagin, the largest polyphenol among ellagitannins with a molecular weight of 1084 grams per mole, constitutes more than half of the total antioxidant capacity and is present predominantly in pomegranate tissues including flowers.<sup>[1]</sup> Ellagitannins are hydrolyzable tannins that yield ellagic acid upon hydrolysis and are subsequently metabolized by gut microbiota into urolithins,

particularly urolithin A, which exhibit enhanced bioavailability and biological activity.<sup>[2]</sup>

Anthocyanins, water-soluble phenolic pigments, have been quantified in pomegranate flower extracts at concentrations suitable for commercial applications.<sup>[3]</sup> The major anthocyanins identified in pomegranate include cyanidin-3,5-diglucoside and delphinidin-3,5-diglucoside, which contribute to the characteristic red-orange coloration.<sup>[4]</sup> Flavonoids, including quercetin derivatives, catechins, and rutin, along with phenolic acids such as gallic acid, chlorogenic acid, and caffeic acid, constitute additional bioactive components with synergistic antioxidant properties.<sup>[1]</sup>

**Table 2: Major Phytochemical Constituents of *Punica granatum* Flower.**

Phytochemical Class	Specific Compounds	Concentration/Content	Primary Functions
Ellagitannins	Punicalagin, punicalin, pedunculagin	Predominant class	Potent antioxidant, anti-inflammatory, anticancer
Ellagic Acid	Free and conjugated forms	Released from ellagitannins	ROS scavenging, metal chelation
Anthocyanins	Cyanidin-3,5-diglucoside, delphinidin-3,5-diglucoside	Variable concentrations	Antioxidant, vascular protection
Flavonoids	Quercetin, rutin, catechin, kaempferol	Moderate levels	Anti-inflammatory, antioxidant
Phenolic Acids	Gallic acid, chlorogenic acid, caffeic acid	Variable concentrations	Free radical scavenging, enzyme inhibition
Metabolites	Urolithin A, urolithin B (gut microbiota products)	Post-ingestion formation	Enhanced bioavailability, neuroprotection

\*Source:<sup>[1-5]</sup>\*

### 2.4.2 Antioxidant Mechanisms of Action

The antioxidant mechanisms of pomegranate phytochemicals operate through multiple complementary pathways that collectively provide comprehensive protection against oxidative stress. Punicalagin directly scavenges reactive oxygen species including superoxide radicals, hydrogen peroxide, and hydroxyl radicals while simultaneously exhibiting metal chelating ability by binding transition metals such as ferrous ( $Fe^{2+}$ ) and copper ( $Cu^{2+}$ ) ions, thereby blocking Fenton reaction-mediated hydroxyl radical formation.<sup>[11]</sup> In vascular endothelial cells, pomegranate polyphenols activate endothelial nitric oxide synthase (eNOS), promoting

nitric oxide synthesis that acts as a superoxide scavenger and maintains redox homeostasis.<sup>[11]</sup>

Pomegranate polyphenols activate the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway through inactivation of Kelch-like ECH-associated protein 1 (Keap1), resulting in nuclear translocation of Nrf2 and subsequent upregulation of antioxidant response element (ARE)-driven genes including heme oxygenase-1, superoxide dismutase, and glutathione peroxidase.<sup>[12]</sup> Ellagitannins demonstrate superior efficacy in protecting low-density lipoproteins from oxidation compared to other natural antioxidants,

interrupting lipid peroxidation chain reactions and preventing foam cell formation.<sup>[13]</sup> The bioavailability of ellagitannins is enhanced through gut microbiota-

mediated conversion to urolithins, which exhibit prolonged circulation time and enhanced cellular uptake compared to parent compounds.<sup>[2]</sup>

**Table 3: Antioxidant Mechanisms of Pomegranate Bioactive Compounds.**

Mechanism of Action	Bioactive Compound	Molecular Target	Biological Outcome
<b>Direct ROS Scavenging</b>	Punicalagin, ellagic acid, anthocyanins	Superoxide, H <sub>2</sub> O <sub>2</sub> , hydroxyl radicals	Neutralization of free radicals
<b>Metal Chelation</b>	Punicalagin, ellagic acid	Fe <sup>2+</sup> , Cu <sup>2+</sup> transition metals	Prevention of Fenton reaction
<b>eNOS Activation</b>	Polyphenolic compounds	Endothelial nitric oxide synthase	NO production, vascular protection
<b>Nrf2 Pathway Activation</b>	Ellagitannins	Keap1/Nrf2/ARE axis	Upregulation of antioxidant enzymes
<b>Lipid Peroxidation Inhibition</b>	Polyphenolic complex	Membrane lipids, LDL particles	Protection from oxidative modification
<b>Enhanced Bioavailability</b>	Urolithin A, urolithin B	Cellular membranes	Improved absorption and efficacy

Source:<sup>[11,12,2,13]</sup>

### 2.4.3 Reported Health Benefits

**Cardiovascular Protection:** Pomegranate consumption demonstrates significant cardiovascular protective effects through multiple mechanisms including blood pressure reduction, lipid profile improvement, and atherosclerosis attenuation. Clinical trials in patients with at least one cardiovascular risk factor consuming pomegranate juice (240 milliliters per day for one year) showed progressive carotid intima-media thickness reduction of 13, 22, 26, and 35 percent after 3, 6, 9, and 12 months respectively, while control groups experienced 10 percent thickness increase.<sup>[14]</sup> Pomegranate extracts significantly reduce systolic and diastolic blood pressure through improved nitric oxide bioavailability and reduced oxidative stress, with consistent interleukin-6 reduction indicating anti-inflammatory mediation of vascular effects.<sup>[1]</sup> The polyphenolic constituents protect both low-density and high-density lipoproteins from oxidation more effectively than other natural antioxidants, reducing foam cell formation and atherosclerotic plaque development.<sup>[13]</sup>

**Anti-inflammatory Effects:** Anti-inflammatory effects of pomegranate are mediated through suppression of pro-inflammatory cytokines including tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , interleukin-6, and transforming growth factor- $\beta$ , along with cyclooxygenase-2 enzyme inhibition.<sup>[34]</sup>

**Neuroprotective Effects:** In neuroinflammatory contexts, pomegranate extracts reduce beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) gene expression, attenuate microglial activation surrounding senile plaques, and decrease tau protein phosphorylation in Alzheimer's disease models.<sup>[34]</sup> Neuroprotective mechanisms include reduction of amyloid plaque density, increased brain-derived neurotrophic factor expression, decreased acetylcholinesterase enzyme activity, and suppression of caspase-mediated apoptotic pathways.<sup>[35]</sup> Pomegranate peel extract treatment significantly

decreased brain tumor necrosis factor- $\alpha$  levels induced by amyloid- $\beta$  infusion, demonstrating potent anti-neuroinflammatory effects.<sup>[35]</sup>

### 3. *Hibiscus sabdariffa* L. (Roselle)

#### 3.1 Botanical Description and Calyx Characteristics

*Hibiscus sabdariffa* Linn., commonly known as roselle or karkadeh, belongs to the family Malvaceae and is characterized as an annual or perennial herbaceous shrub reaching heights of 1.5 to 3 meters with glabrous reddish stems and deeply 3 to 5 lobed leaves.<sup>[29]</sup> The most commercially valuable part is the fleshy calyx, which develops after flowering as thick, succulent sepals that are bright red to deep crimson in color, measuring 3 to 5 centimeters in length with a characteristic tart acidic flavor attributed to high organic acid content including hibiscus acid, citric acid, and malic acid.<sup>[7]</sup>

#### 3.2 Geographical Distribution and Cultivation in Yemen

*Hibiscus sabdariffa* is cultivated in Yemen primarily in the Tihama coastal plains and southwestern highlands, particularly in Hodeidah, Taiz, and Ibb governorates, where warm tropical to subtropical climates provide optimal growing conditions.<sup>[28]</sup> The crop is traditionally grown as a rain-fed annual during the main season from May to October, with harvesting occurring approximately six months after sowing when calyces reach maximum size and deep red coloration.<sup>[29]</sup>

#### 3.3 Traditional Uses in Yemen for Medicinal and Nutritional Purposes

*Hibiscus sabdariffa* holds significant cultural and medicinal importance in Yemeni traditional medicine, with the dried calyces prepared as a refreshing beverage (karkadeh) consumed both hot and cold for its purported health-promoting properties.<sup>[36]</sup> The calyx infusion is traditionally used as a diuretic, antihypertensive agent, and digestive tonic, with regular consumption believed to reduce blood pressure and support cardiovascular

health.<sup>[36]</sup> In folk medicine, roselle preparations are employed for treating febrile conditions, reducing body temperature during fever, and alleviating symptoms of respiratory tract infections including cough and sore throat.<sup>[37]</sup> The plant also serves nutritional purposes, with young leaves consumed as cooked vegetables rich in

vitamins and minerals, while seeds are occasionally roasted as a coffee substitute.<sup>[7]</sup> Traditional healers prescribe roselle extracts for managing metabolic disorders including obesity and hyperlipidemia, with the acidic beverage valued for its appetite-stimulating and digestive-enhancing properties.<sup>[6]</sup>

**Table 4: Traditional Medicinal and Nutritional Uses of *Hibiscus sabdariffa* in Yemen.**

Plant Part	Traditional Uses	Preparation Method	Therapeutic Indications
<b>Dried Calyces</b>	Antihypertensive, diuretic, fever reduction	Hot/cold aqueous infusion (karkadeh tea)	Hypertension, fluid retention, febrile conditions
<b>Calyx Beverage</b>	Digestive tonic, appetite stimulant, cooling agent	Sweetened or unsweetened infusion	Dyspepsia, loss of appetite, heat exhaustion
<b>Fresh Calyces</b>	Blood purification, metabolic support	Fresh juice extraction	Obesity, hyperlipidemia, detoxification
<b>Young Leaves</b>	Nutritional vegetable, vitamin source	Cooked as leafy vegetable	Nutritional supplementation, anemia
<b>Seeds</b>	Coffee substitute, mild stimulant	Roasted and ground	Beverage preparation, energy boost
<b>Flowers</b>	Respiratory support, antimicrobial	Flower decoction	Cough, sore throat, respiratory infections

Source:<sup>[36,37,7,28]</sup>

### 3.4 Phytochemistry of *Hibiscus sabdariffa*

#### 3.4.1 Major Constituents

*Hibiscus sabdariffa* calyces contain a complex array of bioactive phytochemicals, with anthocyanins representing the predominant class responsible for the characteristic deep red coloration and significant pharmacological activities. The major anthocyanins identified are delphinidin-3-O-sambubioside, constituting the most abundant pigment, and cyanidin-3-O-sambubioside as the second most prevalent, with total anthocyanin content ranging from 1.7 to 2.5 percent of dry weight.<sup>[8]</sup> These anthocyanins are derived primarily from delphinidin and cyanidin aglycones conjugated with sambubioside sugar moieties, along with minor glycosides including delphinidin-3-glucoside and cyanidin-3-glucoside.<sup>[9]</sup>

Organic acids constitute another major phytochemical class in roselle calyces, dominated by hibiscus acid, a stereoisomer of hydroxycitric acid with an additional

hydroxyl group at the second carbon position, comprising up to 14 percent of calyx dry weight.<sup>[37]</sup> Citric acid and malic acid are present in substantial concentrations, with tartaric acid sometimes reaching up to 80 percent in certain varieties, while oxalic, succinic, and ascorbic acids occur in moderate amounts.<sup>[37]</sup> Vitamin C content in fresh or dried calyces has been reported as high as 280 milligrams per 100 grams, exceeding many conventional sources.<sup>[37]</sup>

The polyphenolic profile includes chlorogenic acid and its isomers (neochlorogenic acid and cryptochlorogenic acid) as predominant phenolic acids, along with protocatechuic acid, with chlorogenic acid quantified at approximately 2.7 milligrams per gram in leaf extracts.<sup>[10]</sup> Flavonoid constituents include quercetin, kaempferol, and their glycosides, particularly gossypitrin, hibiscitrin, and sabdaritrin, along with 5-hydroxymethylfurfural as a notable non-anthocyanin compound.<sup>[10]</sup>

**Table 5: Major Phytochemical Constituents of *Hibiscus sabdariffa* Calyces.**

Phytochemical Class	Specific Compounds	Concentration/Content	Primary Functions
<b>Anthocyanins</b>	Delphinidin-3-O-sambubioside (major), cyanidin-3-O-sambubioside	1.7-2.5% dry weight	Antioxidant, natural colorant, cardioprotective
<b>Organic Acids</b>	Hibiscus acid, citric acid, malic acid, tartaric acid	Hibiscus acid up to 14%, tartaric up to 80%	Antioxidant, flavor, chelation
<b>Vitamin C</b>	Ascorbic acid	Up to 280 mg/100g	Antioxidant, immune support
<b>Phenolic Acids</b>	Chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, protocatechuic acid	~2.7 mg/g chlorogenic acid	Anti-inflammatory, antioxidant
<b>Flavonoids</b>	Quercetin, kaempferol, gossypitrin, hibiscitrin, sabdaritrin	Variable concentrations	Vascular protection, enzyme inhibition
<b>Other Compounds</b>	5-Hydroxymethylfurfural, carotenoids (lutein, $\beta$ -carotene)	Moderate levels	Antioxidant, nutritional value

\*Source.<sup>[8-10,37]</sup>\*

### 3.4.2 Antioxidant Mechanisms of Action

The antioxidant mechanisms of *Hibiscus sabdariffa* bioactive compounds operate through multiple synergistic pathways that provide comprehensive cellular protection against oxidative stress. Roselle extract demonstrates potent reactive oxygen species scavenging capacity, directly neutralizing superoxide radicals, hydrogen peroxide, and hydroxyl radicals through electron donation by polyphenolic hydroxyl groups.<sup>[15]</sup> The extract activates the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway, a master regulator of cellular antioxidant defense, resulting in nuclear translocation of Nrf2 and subsequent upregulation of phase II detoxifying enzymes including glutamate-cysteine ligase modifier subunit, heme oxygenase-1, glutathione peroxidase, and glutathione S-transferase.<sup>[38]</sup>

In oxidative stress models, *Hibiscus sabdariffa* extract significantly enhances antioxidant enzyme activities including superoxide dismutase, catalase, and glutathione peroxidase while simultaneously restoring depleted reduced glutathione levels.<sup>[37]</sup> The extract exhibits superior free radical scavenging ability compared to vitamin C in various assays, attributed to the diverse chemical structures of its polyphenolic constituents that facilitate efficient electron donation.<sup>[15]</sup> Anthocyanins, particularly delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside, function as potent antioxidants through multiple mechanisms including direct radical scavenging, metal chelation, and inhibition of lipid peroxidation.<sup>[39]</sup> The organic acid content, especially hibiscus acid and citric acid, contributes to antioxidant activity through metal chelation, preventing Fenton reaction-mediated hydroxyl radical formation.<sup>[7]</sup>

**Table 6: Antioxidant Mechanisms of *Hibiscus sabdariffa* Bioactive Compounds.**

Mechanism of Action	Bioactive Compound	Molecular Target	Biological Outcome
Direct ROS Scavenging	Anthocyanins, polyphenols, vitamin C	Superoxide, H <sub>2</sub> O <sub>2</sub> , hydroxyl radicals	Neutralization of free radicals
Nrf2/HO-1 Pathway Activation	Polyphenolic compounds	Nrf2 transcription factor, ARE genes	Upregulation of antioxidant enzymes
Antioxidant Enzyme Enhancement	Total extract	SOD, CAT, GPx, GST	Increased enzymatic antioxidant defense
GSH Restoration	Anthocyanins, phenolic acids	Glutathione synthesis pathway	Replenishment of cellular antioxidant reserves
Metal Chelation	Organic acids, polyphenols	Fe <sup>2+</sup> , Cu <sup>2+</sup> transition metals	Prevention of Fenton reaction
Lipid Peroxidation Inhibition	Anthocyanins	Membrane lipids	Protection from oxidative damage
Anti-inflammatory	Chlorogenic acid, anthocyanins	NF-κB pathway, inflammatory cytokines	Reduced oxidative stress-induced inflammation

Source:<sup>[15,38,37,39]</sup>

### 3.4.3 Reported Health Benefits

#### Antihypertensive

**Effects:** *Hibiscus sabdariffa* demonstrates significant antihypertensive effects through multiple complementary mechanisms, with clinical trials establishing its efficacy comparable to conventional pharmaceutical interventions. The antihypertensive potential originates from vasodilator activity, diuretic efficacy, functionality as an angiotensin-converting enzyme (ACE) inhibitor, and heart rate reduction ability.<sup>[15]</sup> Clinical studies in mild to moderate hypertensive patients showed that roselle extract reduced serum ACE and plasma aldosterone levels with equal efficacy as lisinopril, with these actions attributed to anthocyanin content.<sup>[40]</sup> The extract promotes vasodilation through enhanced nitric oxide bioavailability and reduced systemic vascular resistance, while diuretic effects contribute to blood pressure reduction through decreased extracellular fluid volume.<sup>[36]</sup>

**Hepatoprotective Effects:** Hepatoprotective effects of *Hibiscus sabdariffa* have been extensively documented in experimental models of liver damage and metabolic dysfunction. In high-fat diet-induced obesity

models, roselle extract significantly reduced liver cholesterol and triglyceride levels that were elevated by dietary challenge, with dose-dependent efficacy comparable to purified anthocyanin treatment.<sup>[41]</sup> The extract enhanced serum paraoxonase-1, an antioxidant liver enzyme that regulates lipid peroxides and protects organs from oxidation-associated damage, while significantly reducing markers of liver damage including alanine aminotransferase and aspartate aminotransferase.<sup>[41]</sup> In tamoxifen-induced hepatotoxicity models, roselle leaf extract demonstrated hepatoprotective effects through reduction of oxidative stress markers, restoration of antioxidant enzyme activities, and normalization of liver enzyme levels.<sup>[37]</sup>

#### Hypocholesterolemic

**Effects:** Hypocholesterolemic effects manifest through multiple pathways including enhanced high-density lipoprotein cholesterol levels, reduced low-density lipoprotein cholesterol, decreased total cholesterol, and diminished triglyceride concentrations in both animal models and human clinical trials.<sup>[41]</sup> The extract reduces hepatic cholesterol synthesis, enhances cholesterol catabolism, and increases fecal bile acid excretion, while anthocyanins inhibit

adipocyte differentiation and reduce fat accumulation.<sup>[15]</sup> Four-week administration of roselle extract in human volunteers efficiently reduced serum cholesterol levels, demonstrating translational efficacy from preclinical to clinical settings.<sup>[41]</sup>

#### 4. Rationale for Combining *Punica granatum* Flower and *Hibiscus sabdariffa* Extracts

##### 4.1 Concept of Polyherbal Antioxidant Combinations

Polyherbal combinations combine multiple botanical extracts to achieve synergistic effects where combined biological activity exceeds the sum of individual components.<sup>[42]</sup> This synergism arises from antioxidant regeneration through redox cycling and the complementary action of direct antioxidants that scavenge reactive oxygen species and indirect antioxidants that activate cellular defense pathways for sustained gene induction effects.<sup>[43,44]</sup> The fractional inhibitory concentration index quantifies synergistic

interaction, with values below 0.5 indicating strong synergy, and polyherbal combinations consistently demonstrate superior efficacy through multi-component interactions among diverse polyphenolic compounds.<sup>[42,45]</sup>

##### 4.2 Complementary Phytochemical Profiles

Pomegranate provides predominantly ellagitannins (particularly punicalagin) while hibiscus contributes primarily anthocyanins (delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside) and organic acids, enabling synergistic interaction as pomegranate's tannins biotransform to urolithins with enhanced bioavailability while hibiscus anthocyanins provide immediate antioxidant effects.<sup>[46,2]</sup> Combined extracts demonstrate significantly higher antioxidant activity with lower half-maximal inhibitory concentration values than individual components through diverse chemical structures facilitating electron donation via different pathways.<sup>[45,47]</sup>

**Table 7: Complementary Phytochemical Profiles.**

Phytochemical Class	<i>P. granatum</i>	<i>H. sabdariffa</i>	Synergistic Potential
Ellagitannins	Punicalagin (major)	Minimal	Sustained antioxidant, urolithin formation
Anthocyanins	Moderate levels	Delphinidin/cyanidin-3-O-sambubioside (major)	Enhanced ROS scavenging, vascular protection
Organic Acids	Gallic, ellagic acid	Hibiscus, citric, malic acid	Metal chelation, pH modulation
Flavonoids	Quercetin, catechin	Quercetin, gossypitrin	Multiple antioxidant pathways

Source:<sup>[5,46,37]</sup>

##### 4.3 Complementary Mechanisms of Action

Both extracts activate Nrf2 signaling through different mechanisms, with polyphenolic compounds disrupting Keap1-Nrf2 complex enabling nuclear translocation and upregulation of antioxidant genes including heme oxygenase-1, glutathione peroxidase, and superoxide dismutase.<sup>[38,44]</sup> Direct reactive oxygen species

scavenging provides immediate protection while gene induction effects ensure sustained endogenous antioxidant capacity, with metal chelation preventing Fenton reaction-mediated hydroxyl radical formation.<sup>[48,43,7]</sup> Combined treatment attenuates oxidative damage by 75 to 100 percent more effectively than single antioxidants.<sup>[49]</sup>

**Table 8: Complementary Antioxidant Mechanisms.**

Mechanism	<i>P. granatum</i>	<i>H. sabdariffa</i>	Synergistic Outcome
ROS Scavenging	Ellagitannins, polyphenols	Anthocyanins, vitamin C	Enhanced radical neutralization
Nrf2 Pathway	Ellagic acid activates Nrf2	Anthocyanins activate Nrf2/HO-1	Sustained antioxidant gene upregulation
Metal Chelation	Gallic, ellagic acid	Hibiscus, citric acid	Fenton reaction inhibition
Enzyme Enhancement	SOD, CAT, GPx	SOD, CAT, GPx, GST	Amplified enzyme activities

Source:<sup>[44,38,48,43]</sup>

##### 4.4 Enhanced Therapeutic Potential in Oxidative Stress Management

Combined extracts demonstrate enhanced therapeutic potential through synergistic mechanisms addressing cardiovascular protection (carotid intima-media thickness reduction with antihypertensive and angiotensin-converting enzyme inhibitory effects), hepatoprotection (paraoxonase-1 activation with antioxidant enzyme restoration), neuroprotection (amyloid plaque reduction with brain-derived

neurotrophic factor enhancement), and metabolic regulation (anti-adipogenic properties with hypocholesterolemic efficacy).<sup>[14,36,41,35,15]</sup>

**Table 9: Enhanced Therapeutic Potential.**

Domain	Combined Mechanisms	Target Population
Cardiovascular	CIMT reduction + ACE inhibition	Hypertensive, dyslipidemic patients
Hepatoprotection	PON-1 + enzyme restoration	Metabolic syndrome, NAFLD
Neuroprotection	Amyloid reduction + BDNF enhancement	Elderly, cognitive decline risk
Metabolic	Anti-adipogenic + hypocholesterolemic	Obesity, diabetes

Source:<sup>[14,36,41,35,15]</sup>

## 5. DISCUSSION

This review consolidates the phytochemical and pharmacological evidence supporting two medicinal plants with significant antioxidant potential that are cultivated in Yemen and hold prominent positions in traditional medicine. Both *Punica granatum* flower and *Hibiscus sabdariffa* calyx possess diverse arrays of bioactive compounds with well-characterized antioxidant mechanisms.

Pomegranate flowers are dominated by ellagitannins, particularly punicalagin, which constitute the most abundant phytochemical class and provide potent antioxidant activity through multiple mechanisms including direct ROS scavenging, metal chelation, and activation of the Nrf2 signaling pathway.<sup>[1,11,12]</sup> The gut microbiota-mediated conversion of ellagitannins to urolithins enhances their bioavailability and prolongs their biological effects.<sup>[2]</sup> Clinical evidence demonstrates significant cardiovascular protective effects, including reduction of carotid intima-media thickness by up to 35 percent with regular consumption.<sup>[14]</sup>

*Hibiscus sabdariffa* calyces are rich in anthocyanins, primarily delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside, along with organic acids including hibiscus acid and phenolic compounds such as chlorogenic acid. These constituents provide potent antioxidant activity through direct radical scavenging, Nrf2 pathway activation, and metal chelation.<sup>[15,38]</sup> Clinical studies demonstrate antihypertensive effects comparable to lisinopril, along with significant hepatoprotective and hypocholesterolemic properties.<sup>[40,41]</sup>

The complementary phytochemical profiles of these two plants provide a strong scientific rationale for their combined use. Pomegranate provides ellagitannins with sustained antioxidant effects through urolithin formation, while hibiscus contributes immediate-acting anthocyanins and organic acids.<sup>[46,2]</sup> Both activate Nrf2 signaling through different mechanisms, providing amplified and sustained upregulation of endogenous antioxidant enzymes.<sup>[38,44]</sup> Combined treatment has been shown to attenuate oxidative damage by 75 to 100 percent more effectively than single antioxidants.<sup>[49]</sup>

The traditional use of both plants in Yemeni medicine, their local availability, and their established safety profiles make them particularly suitable for developing evidence-based interventions addressing the growing burden of oxidative stress-related non-communicable

diseases in Yemen.<sup>[28,5,50]</sup> Non-communicable diseases account for 42 percent of total deaths in Yemen, with substantial underdiagnosis of conditions like type 2 diabetes highlighting urgent needs for accessible preventive interventions.<sup>[21-23]</sup>

## 6. CONCLUSION

This narrative review provides a comprehensive synthesis of the phytochemistry, antioxidant mechanisms, and health benefits of *Punica granatum* flower and *Hibiscus sabdariffa* calyx, two medicinal plants cultivated in Yemen with significant therapeutic potential. Pomegranate flowers contain ellagitannins that provide sustained antioxidant effects through urolithin formation and have demonstrated cardiovascular protective effects in clinical trials. *Hibiscus sabdariffa* calyces contain anthocyanins and organic acids that provide immediate antioxidant activity and have demonstrated antihypertensive efficacy comparable to standard medications. Their complementary phytochemical profiles and mechanisms of action—combining immediate and sustained antioxidant effects, direct radical scavenging with Nrf2-mediated enzyme upregulation, and metal chelation—provide a strong scientific rationale for polyherbal combinations targeting oxidative stress-related disorders. Both plants are locally available in Yemen, have established safety profiles through centuries of traditional use, and address the growing burden of non-communicable diseases in the region. This evidence base supports the potential of these traditional medicinal plants for evidence-based applications in oxidative stress management.

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