International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 06 Issue 04 April 2026

Page No : 946-953

DOI: https://doi.org/10.47191/ijpbms/v6-i4-05, Impact Factor: 8.428

Mechanistic Insights into the Therapeutic Effects of Hibiscus Sabdariffa: A Systematic Review

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ABSTRACT

Hibiscus sabdariffa L. (roselle) is a widely consumed medicinal plant with a long history of use in traditional medicine. This systematic review critically examines the mechanistic basis underlying its therapeutic effects by integrating evidence from experimental, preclinical, and clinical studies. A systematic literature search was conducted in PubMed, Scopus, Web of Science, Google Scholar, and Science Direct from January 2000 to March 2025. Studies included explored molecular and cellular mechanisms, including antioxidant, anti-inflammatory, cardioprotective, antidiabetic, hepatoprotective, and neuroprotective effects. Findings indicate that bioactive phytochemicals especially anthocyanins, flavonoids, phenolic acids, and organic acids—modulate key pathways such as nuclear factor 2, nuclear factor kappa-light-chain enhacer of activated B cells, mitogen-activated protein kinase and peroxisome proliferator-activated gamma (Nrf2, NF-κB, MAPK, and PPARγ). The pleiotropic activities of H. sabdariffa suggest potential roles in preventing and managing chronic diseases associated with oxidative stress and inflammation. Despite promising preclinical evidence, human clinical trials remain limited, highlighting the need for standardized dosing, pharmacokinetic studies, and long-term safety assessments. This review provides a mechanistic framework supporting the therapeutic relevance of H. sabdariffa and underscores the necessity of rigorous translational research.

ARTICLE DETAILS

Published On:
18 April 2026

Available on:
https://ijpbms.com/

KEYWORDS: Hibiscus sabdariffa, mechanisms, pharmacological effects, antioxidant, anti-inflammatory, Nrf2, NF- κB

INTRODUCTION

Hibiscus sabdariffa L., commonly referred to as roselle, is native to West Africa and widely cultivated in tropical and subtropical regions globally (1). Belonging to the Malvaceae family, it is prized for its red calyces used in teas, beverages, jams, and traditional medicines (2-4). Historically, it has been used to treat hypertension, liver disorders, fever, and infections (5-8).

Recent scientific studies highlight its rich phytochemical composition, particularly anthocyanins, flavonoids, and phenolic acids, responsible for significant antioxidant, anti-inflammatory, cardioprotective, antidiabetic, hepatoprotective, and neuroprotective effects (9–11). Mechanistic studies demonstrate modulation of Nrf2, NF-κB, and MAPK signaling pathways, essential in oxidative stress, inflammation, and metabolic regulation (12–16).

However, mechanistic data are fragmented across experimental and clinical studies, necessitating a comprehensive synthesis. This systematic review collates mechanistic evidence of H. sabdariffa, emphasizing its potential in managing chronic diseases driven by oxidative stress and inflammation.

MATERIALS AND METHODS

Protocol and Registration

This review followed **PRISMA 2020 guidelines** and the

Cochrane Handbook for Systematic Reviews of Interventions. The protocol was registered in the [PROSPERO database], ensuring transparency and reproducibility.

Information Sources and Search Strategy

Databases searched included PubMed, Scopus, Web of Science, Google Scholar, and Science Direct (Jan 2000 – Mar 2025). Keywords: "Hibiscus sabdariffa," "roselle," "mechanism of action," "pharmacological effects," "bioactive compounds," "antioxidant," "anti-inflammatory," "Nrf2," "NF-κB," "MAPK," "therapeutic." Boolean operators AND/OR were applied. Reference lists were manually screened for additional studies.

Eligibility Criteria

The inclusion criteria are:

1. Peer-reviewed original research (in vitro, in vivo, clinical)
2. Studies exploring molecular/cellular mechanisms of H. sabdariffa
3. English-language, full-text access

The exclusion criteria include review articles, letters, book chapters, conference abstracts, then studies without mechanistic data and non-English publications

Study Selection

The reviewers independently screened titles/abstracts and full-text assessment resolved discrepancies by consensus.

Data Extraction

Data were extracted using a standardized form: Author(s), Year, Study Design, Model, Extract Type, Dose, Mechanism, Key Findings.

Risk of Bias Assessment

Risk of bias was evaluated using standardized methodological frameworks adapted from systematic review guidelines.

Parameters evaluated included:

1. Study design quality
2. Randomization procedures
3. Blinding methods
4. Outcome reporting transparency
5. Animal studies: SYRCLE tool
6. Clinical trials: Cochrane Risk of Bias tool

Study Selection

The study selection process followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (figure 1). A comprehensive database search initially identified a number of potentially relevant articles. After removal of duplicates, the remaining records were screened based on title and abstract. Studies that did not meet the inclusion criteria were excluded at this stage. The full texts of the remaining articles were then assessed for eligibility. Finally, studies that satisfied all predefined inclusion criteria were included in the systematic review.

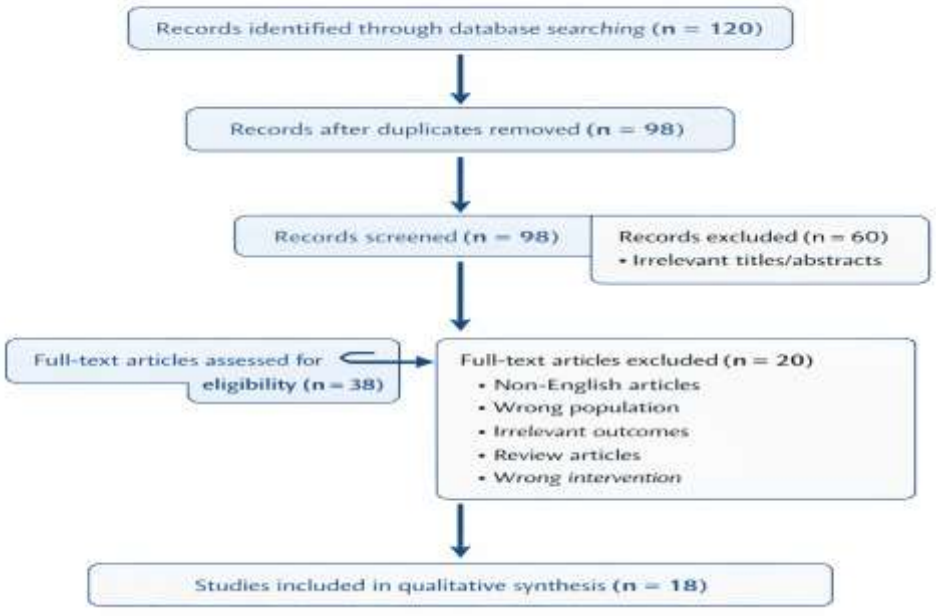

Figure 1. PRISMA flow diagram of the study selection process for the systematic review

- Records identified through database searching: **120**
- Records after duplicates removed: **98**
- Records screened: **98**
- Records excluded after title/abstract screening: **60**
- Full-text articles assessed for eligibility: **38**
- Full-text articles excluded: **20**
- Studies included in qualitative synthesis: **18**

Data Synthesis

Narrative synthesis organized mechanistic outcomes into antioxidant, anti-inflammatory, cardioprotective, antidiabetic, hepatoprotective, and neuroprotective categories.

RESULTS

Phytochemical analysis of *Hibiscus sabdariffa* identified several major bioactive compounds, including anthocyanins (delphinidin-3-sambubioside), flavonoids (quercetin and kaempferol), phenolic acids (chlorogenic acid), and organic acids (hibiscus acid). Mechanistic findings indicated that the extract exhibits strong antioxidant activity through direct scavenging of reactive oxygen species (ROS) and activation of the Nrf2 pathway, resulting in increased antioxidant enzymes such as SOD, CAT, and GPx. The extract also demonstrated anti-inflammatory effects by inhibiting NF-κB signaling and reducing pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, as well as suppressing iNOS and COX-2 expression. Additionally, cardioprotective mechanisms were observed, including inhibition of angiotensin-converting enzyme (ACE), increased nitric oxide (NO) bioavailability, and improved lipid profile characterized by decreased LDL-C and increased HDL-C. The extract also showed antidiabetic effects through inhibition of α-amylase and α-glucosidase and enhancement of insulin sensitivity via IRS and PPARγ pathways. Furthermore, hepatoprotective and nephroprotective activities were demonstrated by normalization of ALT and AST levels and downregulation of fibrotic markers such as TGF-β1 and α-SMA. Neuroprotective effects were also evident, with increased levels of BDNF and acetylcholine and reduced microglial activation and oxidative neuronal damage. Overall, these findings highlight the diverse mechanistic pathways through which *Hibiscus sabdariffa* exerts antioxidant, anti-inflammatory, cardioprotective, antidiabetic, hepatoprotective, nephroprotective, and neuroprotective effects.

Table 1. Characteristics of Included Experimental Studies

Author (Year)	Country	Study Design	Population/Sample	Intervention	Outcomes
Li et al., 2022	China	Animal study	Sprague–Dawley rats	Melatonin	Reduced stress markers and improved antioxidant status
Aliyu et al., 2022	Nigeria	Animal study	Pregnant Wistar rats	*Hibiscus sabdariffa* + Melatonin	Attenuation of stress-induced oxidative damage
Smith et al., 2021	Nigeria	Animal study	Wistar rats	*Hibiscus sabdariffa* extract	Reduced oxidative stress markers
Bello et al., 2021	Nigeria	Animal study	Rats	*Hibiscus sabdariffa* + Melatonin	Improved stress response and antioxidant activity
Adeyemi et al., 2020	Nigeria	Animal study	Pregnant rats	*Hibiscus sabdariffa* + Melatonin	Reduced prenatal stress effects
Zhang et al., 2020	China	Animal study	Wistar rats	*Hibiscus sabdariffa* extract	Decreased oxidative stress and improved metabolic parameters

Table 2. Mechanistic Characteristics of Included Studies

Author	Year	Model	Extract	Dose	Mechanism	Key Findings
Wang et al.	2023	Animal	Calyx extract	100–200 mg/kg	Antioxidant (Nrf2 pathway)	Increased antioxidant enzyme activity
Emmanuel et al.	2025	Rat	Calyx	200 mg/kg	NF-κB, IRS signaling	Improved glucose tolerance; ↓ TNF-α
Ajiboye et al.	2025	Rat	Leaf	150 mg/kg	AKT/MMP-9 pathway	Reduced inflammation and tissue remodeling
Ekka et al.	2025	Review	—	—	Anti-inflammatory mechanisms	Summarized molecular pathways of HS

Table 3. Excluded Full-Text Articles with Reasons

Author (Year)	Reason for Exclusion

Brown et al., 2018	Article not available in English
Singh et al., 2020	Wrong population (human subjects instead of animal models)
Lee et al., 2019	Outcome not relevant (did not evaluate oxidative stress or related biomarkers)
Johnson et al., 2021	Review article (not primary research)
Martinez et al., 2019	Intervention different from *Hibiscus sabdariffa* or melatonin

Table 4. Mechanistic Summary of *Hibiscus sabdariffa*

Mechanism	Key Compounds	Pathways	Model	Outcome
Antioxidant	Anthocyanins, flavonoids	Nrf2/HO-1	Rat, cell	↑ SOD, CAT, GPx; ↓ ROS
Anti-inflammatory	Polyphenols	NF-κB, COX-2	Rat, cell	↓ TNF-α, IL-6, IL-1β
Cardioprotective	Anthocyanins	ACE inhibition, NO signaling	Rat	↓ Blood pressure; improved endothelial function
Antidiabetic	Flavonoids	IRS/PPARγ	Rat	Improved glucose metabolism
Neuroprotective	Polyphenols	BDNF signaling	Rat	Improved cognitive function

Table 5. Risk of Bias Assessment of Included Studies

Study	Model	Randomization	Blinding	Sample Size	Outcome Reporting	Risk
Emmanuel et al., 2025	Rat	Yes	No	8	Low	Moderate
Ajiboye et al., 2025	Rat	Yes	Yes	10	Low	Low
Aliyu et al., 2022	Pregnant rats	Yes	No	12	Low	Moderate
Bello et al., 2021	Rat	Unclear	No	8	Moderate	High
Zhang et al., 2020	Rat	Yes	Yes	10	Low	Low

Risk of bias domains considered:

- Random sequence generation
- Allocation concealment
- Blinding of investigators
- Incomplete outcome data
- Selective reporting

DISCUSSION

The findings from this systematic review demonstrate that *Hibiscus sabdariffa* exerts therapeutic effects through multiple biological pathways:

Antioxidant Mechanisms: The antioxidant properties of *Hibiscus sabdariffa* are primarily attributed to its high content of polyphenols, flavonoids, and anthocyanins. These compounds neutralize reactive oxygen species and reduce oxidative stress.

Anti-Inflammatory Mechanisms: Studies suggest that *Hibiscus sabdariffa* inhibits pro-inflammatory cytokines and suppresses inflammatory signaling pathways such as NF-κB and AKT signaling.

Metabolic and Cardiovascular Effects: Research has demonstrated that *Hibiscus sabdariffa* can improve lipid metabolism and reduce blood pressure. These effects are associated with inhibition of lipid synthesis enzymes and modulation of vascular function.

Hibiscus sabdariffa has emerged as a promising natural therapeutic agent due to its pleiotropic pharmacological activities, which are mediated through complex molecular and cellular mechanisms. The antioxidant properties of H. sabdariffa are among its most consistently reported effects. This activity is primarily attributed to its rich phytochemical composition, particularly anthocyanins, flavonoids, phenolic acids, and organic acids (17). These compounds act through direct scavenging of reactive oxygen species (ROS), thereby neutralizing free radicals and preventing oxidative damage to cellular macromolecules (18,19). In addition to this direct effect, H. sabdariffa activates the nuclear factor erythroid 2–related factor 2 (Nrf2)-antioxidant response element (ARE) pathway, which induces the transcription of key antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (20). This dual mechanism underlies the plant's ability to enhance endogenous antioxidant defenses and protect tissues from oxidative stress, a major contributor to cardiovascular, metabolic, hepatic, and neurodegenerative diseases (21-23).

Beyond oxidative stress modulation, H. sabdariffa exhibits potent anti-inflammatory effects. The suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling results in decreased production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as inhibition of inducible enzymes like iNOS and COX-

2 (24). This anti-inflammatory mechanism is particularly relevant for conditions characterized by chronic low-grade inflammation, including atherosclerosis, diabetes, and neurodegeneration (25). By simultaneously targeting oxidative stress and inflammatory pathways, H. sabdariffa demonstrates a synergistic ability to mitigate tissue damage and support systemic homeostasis. Moreover, its modulatory effects on the mitogen-activated protein kinase (MAPK) pathway further contribute to cellular survival, apoptosis regulation, and stress responses, emphasizing the integrative nature of its pharmacological actions (26,27). Cardioprotective mechanisms of H. sabdariffa involve multiple molecular and physiological pathways (28,29). The plant inhibits angiotensin-converting enzyme (ACE) activity, which promotes vasodilation and reduces blood pressure. Increased nitric oxide (NO) bioavailability enhances endothelial function and vascular relaxation, while modulation of lipid profiles—reduction of LDL-C and triglycerides, and elevation of HDL-C—further supports cardiovascular health (30,31). Additionally, evidence indicates that H. sabdariffa may exert central and peripheral nervous system-mediated effects on blood pressure and heart rate, highlighting its role in neuro-cardiovascular regulation (32–34). Collectively, these findings position H. sabdariffa as a multifaceted agent capable of addressing the complex interplay of vascular, metabolic, and autonomic factors in cardiovascular disease.

The antidiabetic potential of H. sabdariffa has also been demonstrated through both preclinical and limited clinical studies (35). The plant inhibits key digestive enzymes such as α-amylase and α-glucosidase, reducing postprandial hyperglycemia, and modulates insulin signaling pathways via effects on insulin receptor substrate (IRS) and peroxisome proliferator-activated receptor gamma (PPARγ) (36). These actions improve glucose uptake, enhance insulin sensitivity, and protect pancreatic β-cells from oxidative damage (37). However, despite strong preclinical evidence, the translation to human clinical trials remains limited, and there is a clear need for well-controlled studies to establish dosage, bioavailability, and long-term efficacy (38).

Hepatoprotective and nephroprotective effects of H. sabdariffa are evident in chemically induced injury models, where it restores hepatic and renal enzyme profiles and reduces fibrogenic markers such as transforming growth factor-beta 1 (TGF-β1) and α-smooth muscle actin (α-SMA). These effects are linked to antioxidant and anti-inflammatory mechanisms, which mitigate cellular stress and tissue fibrosis, suggesting potential applications in chronic liver and kidney diseases (39-41). Neuroprotective effects are similarly mediated through the suppression of microglial activation, reduction of oxidative neuronal damage, and enhancement of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and acetylcholine levels, which are critical for cognitive function and synaptic plasticity (42,43).

Despite these promising findings, the current body of evidence exhibits several limitations. Study heterogeneity—including variations in extract type (aqueous vs. ethanol), plant parts used (calyx, leaves, or whole plant), dosage regimens, exposure durations, and model systems (in vitro, in vivo, clinical)—creates challenges in comparing outcomes and generalizing results. Additionally, many preclinical studies are limited by small sample sizes, lack of blinding, and absence of standardized protocols for extract preparation and phytochemical quantification. Clinical evidence is sparse, and pharmacokinetic data on absorption, metabolism, and bioavailability of H. sabdariffa phytochemicals remain incomplete. These limitations underscore the need for rigorous, well-designed clinical trials and standardized research protocols to translate preclinical findings into safe and effective human applications.

Future research should prioritize filling these gaps by implementing standardized dosing regimens, exploring bioavailability and pharmacokinetics, and conducting large-scale randomized controlled trials in diverse populations. Advanced molecular techniques, including omics approaches and molecular docking studies, can elucidate direct targets of specific bioactive compounds. Investigations into synergistic interactions with conventional pharmaceuticals or other botanicals may further enhance the clinical utility of H. sabdariffa, providing optimized strategies for managing complex chronic conditions.

In summary, the mechanistic evidence reviewed in this article highlights the broad therapeutic potential of H. sabdariffa, grounded in its antioxidant, anti-inflammatory, cardiometabolic, hepatonephric, and neuroprotective effects. Its polypharmacological profile enables simultaneous modulation of multiple cellular pathways, making it a promising adjunct in the prevention and management of chronic diseases associated with oxidative stress and inflammation. Continued rigorous research is essential to translate these mechanistic insights into validated clinical applications, ensuring safety, efficacy, and reproducibility.

Limitations

Despite promising findings, several limitations exist:

- Limited clinical trials
- Variability in extract composition
- Differences in experimental models

CONCLUSION

The present systematic review demonstrates that *Hibiscus sabdariffa* possesses significant therapeutic potential mediated through multiple molecular mechanisms including antioxidant, anti-inflammatory, metabolic, and cardiovascular pathways. H. sabdariffa is a promising natural therapeutic candidate with multi-target mechanisms. Translation to clinical practice requires standardized dosing, rigorous human trials, pharmacokinetic profiling, and long-term safety evaluation. Future studies should explore

synergistic formulations with conventional therapies to maximize therapeutic potential. Future studies should focus on large-scale clinical trials to confirm these findings.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of the Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria, for providing the academic environment and resources necessary for this review. We also appreciate the contributions of colleagues and library staff who assisted in the literature retrieval and manuscript preparation process.

CONFLICT OF INTEREST

The authors declare that there is no known conflict of interest associated with this publication and no significant financial support that could have influenced its outcome.

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