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Harnessing Functional Foods and Medicinal Plants for Managing Sickle Cell Anaemia in Nigeria: A Review

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ABSTRACT

Haemoglobinopathies are inherited erythrocytes' dysfunctions, caused by autosomal genetic changes like a single nucleotide change in a gene or the decreased production of at least one globin chain that result in unbalanced haemoglobin synthesis, anaemia and other complications. The diseases can be managed through blood transfusion or use of approved conventional therapeutics like hydroxyurea, voxelotor, crizanlizumab, L-glutamine, L-arginine and nutritional supplements. However, these are either unaffordable to majority of people with the disease or pose some side effects, which compel patients to resort to use of functional foods and medicinal plants for treatment. These functional foods and medicinal plants in Nigeria are being used to inhibit or reverse sickling of red blood cells by exploiting the allosteric nature of haemoglobin *S* to inhibit it from assuming a tensed state or reverse it from such state. They are also employed to exert significant pain relief in patients. Therefore, this work exploited peer-reviewed articles form PubMed and Google Scholar to harness the functional foods and medicinal plants locally employed by Nigerians in the treatment of the most prevalent erythrocytes' dysfunctions (sickle cell anaemia), indicating their interactions with the structure of haemoglobin and some cellular receptors as well as the potentials of exploiting them for the development of drugs or nutraceuticals with antisickling and anti-nociceptive effects**.** However, despite their promising potentials in sickling management, challenges like bioavailability, inadequate molecular understanding of antisickling pathways and limited clinical evidence remain. Addressing these issues through standardizing phytochemical profiles, deepening the molecular understanding of antisickling pathways and clinical trials is crucial for their effective therapeutic application.

Keywords: Antisickling Activity, Functional Foods, Haemoglobin, Medicinal Plants, Sickle Cell Anaemia.

INTRODUCTION

Haemoglobinopathies are hereditary disorders affecting erythrocytes, resulting from either a point mutation or the reduced production of one or more globin chains. The substitution of glutamate with valine leads to sickle cell anaemia (SCA/Hb*SS*), while substitution with lysine results in haemoglobin C disease (Hb*CC*). Thalassemia, another type of haemoglobinopathy, arises from decreased production of at least one globin chain (α, β, γ, or δ) (Silberstein, 2008; Inusa *et al*., 2019).

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Among these conditions, SCA (Hb*SS*) is the most prevalent and severe (Imaga, 2013; Mangla *et al*., 2023). In Africa, it accounts for 70% of all sickle cell diseases (SCDs) and is characterized by four main pathophysiological processes: haemoglobin polymerization, vaso-occlusion, endothelial dysfunction, and sterile inflammation. These processes lead to clinical symptoms and complications such as anaemia, vaso-occlusive crises, priapism, gallstones and infections (Sundd *et al*., 2019).

SCA is especially common in sub-Saharan Africa, India and the Democratic Republic of Congo (DRC), where 90% of the global population with SCD traits reside (Kadima *et al*., 2015; Adigwe *et al*., 2023). Nigeria has the highest prevalence, with approximately 25% of its population carrying the sickle cell trait (Nwabuko *et al*., 2022; Adigwe *et al*., 2023).

The 2018 Nigerian Demographic and Health Survey (NDHS) indicates that Kogi, Benue and Ekiti States as well as parts of Ondo and Ogun States, show the highest prevalence of SCA, with genotype distributions varying across the six geopolitical zones as shown in table 1 (National Population Commission and ICF, 2019; Pullum, 2020).

Table 1: Percentages of the genotypes of children age 6-59 months in geopolitical zones

Zone	*AA*(%)	AS (%)	*AC* (%)	*SC* (%)	*SS* (%)	Others (%)
North-Central	79.07	17.82	1.76	0.36	0.94	0.05
North-East	78.02	20.47	0.33	0.27	0.91	0.00
North-West	77.56	19.97	1.25	0.16	1.01	0.05
South-East	79.74	19.11	0.00	0.13	1.02	0.00
South-South	80.35	19.09	0.24	0.00	0.32	0.00
South-West	70.81	20.96	5.23	1.60	0.82	0.58
Total	77.20	19.72	1.63	0.44	0.88	0.13

(National Population Commission and ICF, 2019; Pullum, 2020).

SCA involves the following four main pathophysiological mechanisms (Sundd *et al*., 2019) as shown in figure 1:

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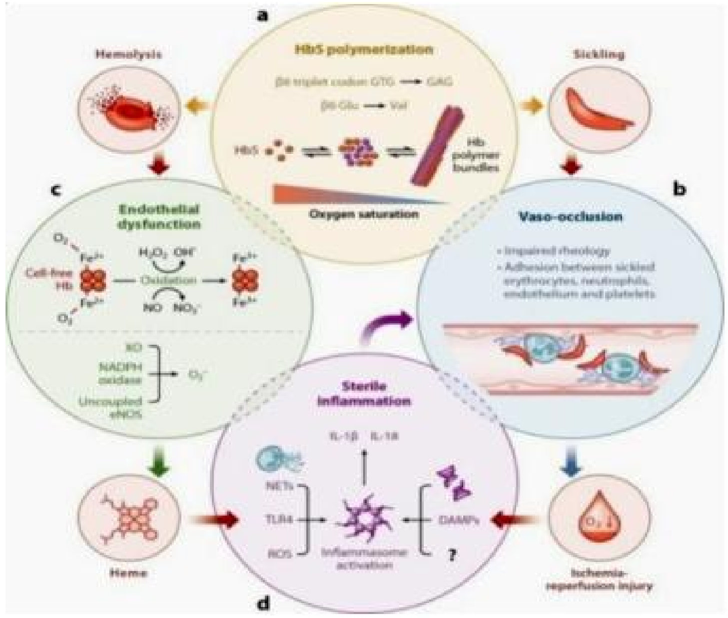

Figure 1: The molecular pathophysiology of sickle cell anaemia (Sundd *et al.,* 2019).

Haemoglobin *S* (Hb*S*) Polymeriztion: Deoxygenated Hb*S* aggregates into rigid fibers, causing the characteristic sickling of red blood cells (RBCs).

Vaso-Occlusion: Blocking of blood vessels, often due to sickled RBCs, leading to reduced blood flow and pain.

Haemolysis-Induced Endothelial Dysfunction: Impaired functioning of the blood vessel's inner lining, which reduces vasodilation, and increases the risk of inflammation and thrombosis.

Sterile Inflammation: Inflammation triggered by non-infectious factors that contributes to the disease's complications.

Its management is a lifelong process aimed at preventing painful episodes, opportunistic infections, anaemia and complications such as delayed puberty, gallstones and priapism (Askinazi *et al*., 2022; Le Page, 2023). Conventional treatments are summarized in table 2.

Table 2: Conventional treatment and management of sickle cell anaemia

S/No.	Treatment	Roles	Reference
1.	Gene therapy	Corrects faulty genes and restore RBCs' functions through clustered regularly interspaced short palindromic repeats and associated protein9 (CRISPR-Cas9). Switch-on genes for Hb*F* production.	Askinazi *et al*., 2022
2.	Blood and Bone Marrow Transplantation	Replaces defective RBCs. Restores normal haematopoiesis	National Heart, Lung and blood Institute, 2023

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3.	Transfusion	Increases the number of normal erythrocytes. Reduces the risk of recurring stroke in patients with a history of acute stroke.	Ware *et al*., 2017; Acharya *et al.*, 2023; National Heart, Lung and blood Institute, 2023
4.	Hydroxyurea	Decreases polymerization of Hb*S* and associated complications. Stimulates the production of Hb*F* or nitric oxide (NO).	Plan, 2008; Ware *et al.*, 2017; Migotsky *et al.*, 2022; Acharya *et al.*, 2023
5.	Vanillin	Decreases Hb*S* polymerization	Abraham *et al.,* 1991
6.	Voxelotor	Inhibits Hb*S* polymerization. Enhances the RBCs' conformation and lengthens its half-life.	Kanter, 2015; Blair, 2020a; Esrick *et al.*, 2021; Bain *et al.*, 2022; Kanter *et al.,* 2022
7.	Crizanlizumab and Heparin Derivatives	Inhibits vascular occlusion	Ballas *et al.* 2012; Blair, 2020b; Acharya *et al.*, 2023
8.	L- Glutamine	Reduces oxidative stress in RBCs to lower endothelial adhesion	Hassell, 2010; Cos *et al.*, 2020; Reddy *et al.,* 2022
9.	L- arginine and Statins	L- arginine generates more endogenous NO to reduce vaso-occlusion. Statins inhibits Rho kinase to stimulate the expression and activity of endothelial NO synthase	Morris *et al.*, 2003; Abboud, 2020; Ashorobi *et al.*, 2022; Pecker *et al.*, 2022
10.	5-Hydroxy-methyl-2-furfural (5-HMF)	Prevents or reduces sickling of RBCs by allosterically altering its affinity for oxygen	Abdulamlik *et al.*, 2004; Shapla *et al.* 2018; Kassa *et al.,* 2019
11.	VZHE-039	Increases oxygen affinity in Hb*S* like in Hb*F*	Abdulmalik *et al.,* 2020
12.	Prasugrel and Apixaban	Prasugrel prevents platelet aggregation brought about by vaso-occlusive episodes. Apixaban blocks Factor Xa to prevent the activation of prothrombin into thrombin.	Brittain *et al.*, 2004; Acharya *et al.*, 2023

In regions where access to conventional treatment is limited, traditional and herbal formulations play a supportive role. Two notable herbal treatments are listed in table 3.

Table 3: Herbal formulations for the management of sickle cell anaemia

S/No	Formulation	Type	Action	Limitation	Reference
1..	Niprisan®	A phytomedicine formulated from Black Pepper seeds, Andaman Redwood stem, Cloves fruits and Guinea Corn leaves.	Inhibits and reverse sickling of RBCs	Expected to have side effects due to its significant inhibition of cytochrome CYP3A4	Obodozie *et al.*, 2010; Ameh *et al.,* 2012; Imaga, 2012; Uwagbale, 2019
2.	Ciklavit®	A nutraceutical formulated from an extract of Pigeon Pea and supplemented with amino acids, vitamins such as Vitamin C and minerals like Zinc.	Induction of Hb*F* production and reversal of sickling to reduce painful episodes associated with the disease	May pose a drug-drug interaction	Morton, 1976; Duke, 1981; Imaga *et al.,* 2013; Akinleye *et al.*, 2016

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Nigeria holds strategic importance in addressing SCDs. According to the World Health Organization (WHO) and Nigeria's Ministry of Health, approximately 25% of Nigerians are carriers of the mutant genes responsible for genetic disorders (National Population Commission and ICF, 2019; Nwabuko *et al*., 2022; Obiezu, 2023). Despite this high prevalence, there is insufficient healthcare policy support for individuals with the diseases (Amarachukwu *et al*., 2022).

This leaves affected individuals burdened with significant economic and financial challenges, including the costs of hospital admissions, medication, blood transfusions and lost of working hours by parents due to the ill health of their children (Olatunya *et al*., 2015).

Further researches are needed to address the challenges faced by SCA patients in Nigeria. Both conventional and traditional treatment approaches have failed to provide adequate solutions. Conventional treatments are often expensive and associated with side-effects. On the other hand, traditional medicines used for managing SCA can pose toxicity risks due to their phytochemicals, and often lacks regulation and scientific validation for efficacy and safety.

This review aimed to highlight functional foods and medicinal plants with antisickling property that can be leveraged in Nigeria for managing the disease or for the development of supplements and phytomedicines.

Functional foods and Medicinal Plants with Antisickling Activity in Nigeria

Nigerians have for long used functional foods and medicinal plants for health care, leveraging their diverse chemical compositions and pharmacological properties. Key components that contribute to their value in phytomedicine include alkaloids, flavonoids, phenolic compounds and terpenes (Edeoga *et al*., 2015).

Functional foods, defined as conventional foods that offer health benefits beyond basic nutrition, play a role in preventing chronic diseases (Food and Agricultural Organization, 2007a; Kotue, 2018). These foods are used for medicinal purposes and healthy living, including SCA management in Nigeria and many other developing countries (Kotue, 2018). Examples include the dark leafy greens, fruits, legumes, grains, herbs and spices highlighted in table 4.

Table 4: Some functional foods in Nigeria with antisickling activity

S/No.	Name of Functional Food	Class of Food	Action	Reference
1.	*Cajanus cajan* (Pigeon Pea/*Waken Bature* in Hausa Language) Seeds	Legume	Supports Hb*F* production	Osuagwu, 2010.
2.	*Xylopia aethiopica* (Negro Pepper/*Kimba* in Hausa Language) Spice	Herb/Spice	Pain relief, immune boosting, anti-inflammatory and antioxidant effects	Uwakwe and Nwaoguikpe, 2008.
3.	*Allium sativum* (Garlic/*Tafarnuwa* in Hausa Language) Bulb	Herb/Spice	Pain relief, immune boosting, anti-inflammatory and antioxidant effects	Takasu *et al.,* 2002; Gbadamosi and Yekini, 2012.
4.	*Curcuma longa* L. (Tumeric/*Kurkur* in Hausa Language) Rhizome	Herb/Spice	Reduces pain through anti-inflammatory and analgesic effects	Gbadamosi, 2017.

5.	*Allium cepa* L.(Onion/*Albasa* in Hausa Language) Bulb	Herb/Spice	Reduces inflammation and combats oxidative stress	Gbadamosi, 2017.
6.	*Brassica oleracea* (Broccoli)	Vegetable	Stabilizes and protects membrane	Akoachere *et al*., 2002.
7.	*Actinidia deliciosa* (Kiwi)	Fruit	Reduces inflammation and combats oxidative stress	Umeakunne and Hibbert, 2019.
8.	*Juglans regia* (Walnut)	Legume	Anti-adhesive, anti-polymerization and anti-inflammatory	Mori and Beilin, 2004.
9.	*Linum usitatissimum* (Flax) Seeds	Legume	Anti-adhesive, anti-polymerization and anti-inflammatory	Mori and Beilin, 2004.
10.	*Salvia hispanica* (Chia) Seeds	Grain	Anti-adhesive, anti-polymerization and anti-inflammatory	Mori and Beilin, 2004.
11.	*Vernonia amygdalina Del.*(Bitter Leaf/ *Shuwaka* in Hausa Language) Leaves	Vegetable	Reduces inflammation and combats oxidative stress	Kunle and Omoregie, 2013.
12.	*Monodora myristica* (African Nutmeg) Spice	Herb/Spice	Analgesic effects	Uwakwe and Nwaoguikpe, 2008.
13.	*Moringa oleifera* (*Zogale* in Hausa Language) Leaves	Vegetable	Reduces inflammation and combats oxidative stress	Haruna and Kankara, 2021.
14.	Camel's milk	Protein	Increased production of Hb*F*	Rukayya *et al.*, 2018.
15.	*Amaranthus hybridus* (Green Amaranth/*Alayyaho* in Hausa Language) Leaves	Vegetable	Supports RBCs production, reduces inflammation and oxidative stress	Haruna and Kankara, 2021.
16.	*Adansoonia digitata* (Baobab/*Kuka* in Hausa Language) Leaves	Fruit	Supports immune system, reduces inflammation and oxidative stress	Adesanya *et al.,* 1998.
17.	*Garcinia kola* (Bitter kola/*Namijin Goro* in Hausa Language) Leaves, Seeds and Seed Pods	Herb	Stabilizes and protects membrane	Adejumo *et al.*, 2011.
18.	*Manihot esculenta* (Cassava/*Rogo* in Hausa Language) Leaves	Root Vegetable	Nutritional value as well as Analgesic, anti-inflammatory and antioxidant effects	Haruna and Kankara, 2021.
19.	*Vigna unguiculata* (Cowpea/*Wake* in Hausa Language) Seeds	Legume	Nutritional value as well as immune boosting, anti-inflammatory and antioxidant effects	Mpiana *et al.*, 2008

Medicinal plants, defined as flora used for their therapeutic properties to treat or prevent diseases and promote well-being (Food and Agricultural Organization, 2007b), have been vital for centuries. Modern advancements in medicine have not diminished their use; instead, their application has grown as more people seek natural health solutions (Muhammad and Ibrahim, 2019; Nwaka *et al.,* 2019). Examples are highlighted in table 5.

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Table 5: Some medicinal plants in Nigeria with antisickling activity.

S/NO.	Name of plant and the part used	Action	Reference
1	*Fagara zanthoxypoides* (Artar /*Fasakuwa* in Hausa Language) Roots	Analgesic, anti-inflammatory and antioxidant effects	Ameh *et al*., 2012.
2	*Jatropha tajorensis* (Hospital too far) Leaves	Anti-inflammatory, antioxidant, analgesic, hepato-protective and immune-boosting effects	Haruna and Kankara, 2021.
3.	*Sorghum bicolor* (Guinea Corn/*Daawa* in Hausa Language) Leaves	Supporting RBCs production and providing anti-inflammatory and antioxidant benefits	Mojisola *et al*., 2009.
	Annona senegalensis (Wild Soursop) Leaves	Anti-inflammatory and antioxidant benefits	Takasu *et al.,* 2002.
4.	*Ipomoea batatas* (Sweet Potato) Leaves	Antioxidant and immune support benefits	Ilondu and Enwa, 2013.
5.	*Mucuna pruriens* (Devil Beans) Leaves	Neurological health benefits, anti-inflammatory and antioxidant benefits	Ilondu and Enwa, 2013.
6.	*Terminalia catappa* (Tropical Almond or Indian Almond) Leaves	Reducing oxidative stress and managing pain and inflammation	Ilondu and Enwa, 2013.
7.	*Gossypium hirsutum* (Upland Cotton Tree) Leaves	Managing pain, inflammation and reducing oxidative stress	Ilondu and Enwa, 2013.
8.	*Mongiferaindica* (Mango) Leaves	Managing pain, inflammation and reducing oxidative stress	Ilondu and Enwa, 2013.
9.	*Jatropha curcas* (Barbados Nut) Leaves	Managing pain, inflammation and reducing oxidative stress	Ilondu and Enwa, 2013.
10.	*Phyllanthus amarus Schum*. (Stone Breaker) Leaves and Seeds	Managing pain, inflammation and reducing oxidative stress	Kunle *et al*. 2013.
11.	*Rauwolfia vomitoria Afzel* (African Serpentwood/*Wada* in Hausa Language) Leaves	Managing pain crises and reducing oxidative stress	Abere *et al*., 2014.
12.	*Aloe vera (L.) Burm. f.* (Medicinal Aloe)	Managing pain crises, chronic inflammation and reducing oxidative stress	Gbadamosi and Yekini, 2012.
13.	*Alchornea cordifolia* (Laceleaf or Arrowleaf/*Banbani* in Hausa Language) Leaves	Managing pain crises, chronic inflammation and reducing oxidative stress	Mpiana *et al*., 2007.
14.	*Hymenocardia acida* (Heart Fruits/*Jan Yaro* in Hausa Language) Leaves	Managing pain, inflammation and reducing oxidative stress	Ibrahim *et al*., 2007.
15.	*Parquetina nigrescens* (African Parquetina/*Kwankwani* in Hausa Language) Leaves.	Reversal and inhibition of sickling	Imaga *et al*., 2010.

Mechanisms of Action of Functional Foods and Medicinal Plants in SCA

The pathology of SCA is influenced by the structure of haemoglobin and the role of ion channels, which facilitate ion movement across membranes. These elements are involved in the sensory nervous system's process of encoding pain stimuli (Gupta and Jamieson, 2016; Sundd *et al*., 2019).

Mechanisms of Action in Inhibiting or Reversing Sickling

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Haemoglobin is an allosteric protein (Perrella and Russo, 2003) that can exist in a tensed (T) state when deoxygenated or in a relaxed (R) state when oxygenated, as illustrated in figure 2.

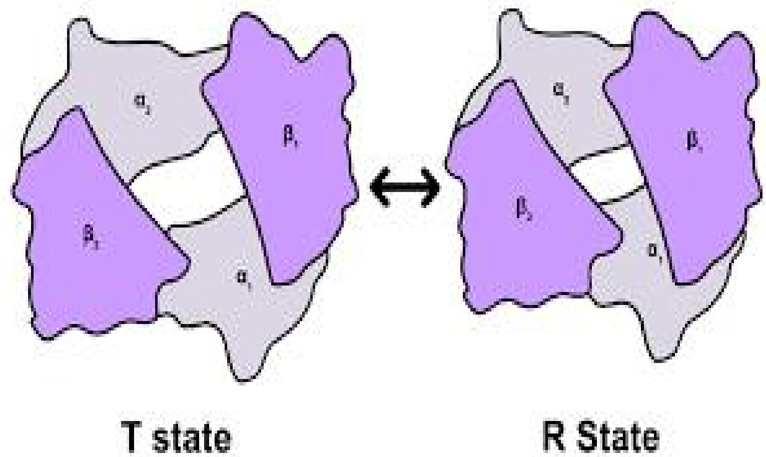

Figure 2: Haemoglobin molecule in the tensed (T) state and relaxed (R) state (Anderson and Hiraki, 2020).

In the T-state, Hb*S* tends to polymerize, leading to the sickling of RBCs when deoxygenated. Bioactive compounds in functional foods and medicinal plants have demonstrated the ability to stabilize Hb*S* in the R-state, enhancing the oxygen affinity of RBCs and reducing rigidity. This stabilization prevents or reverses polymerization and, consequently, sickling (Archer and Brain, 2020). Supporting this, Safo *et al.* (2004) noted that inhibiting or reversing Hb*S* polymerization can prevent sickling crises.

Examples of bioactive compounds that stabilize Hb*S* in the R-state include furfural derivatives (Safo *et al*., 2004; Ameh *et al*., 2011), alternative aspirins such as acetyl-3,5-dibromosalicylic acid (Walder *et al.,* 1977; Ameh *et al.,* 2011), capsaicinoids and some substituted benzaldehydes (Abraham *et al.,* 1991; Nnamani *et al*., 2008; Ameh *et al*., 2011). Other compounds like 2,3-bisphosphoglycerate (2,3-BPG) and various shikimic acid derivatives also contribute to this antisickling effect (Safo *et al*., 2004).

Mechanisms of Action in Ameliorating Pain

Pain is an unpleasant sensation triggered by actual or potential tissue damage and plays a critical role in defense and coordination (Ameh *et al*., 2012). The process involves interplay of ion channels and receptors that prevent prolonged pain beyond its purpose (Ion Channels, 2011).

In SCA patients, pain arises from inflammatory (immune response to harmful stimuli), neuropathic (abnormal signaling from injured axons and nociceptors) and nociceptive (detection and interpretation of harmful stimuli) mechanisms, each generating distinct neurochemical signatures within the

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nervous system (Campbell and Meyer, 2006; Tran *et al*., 2017; Physiopedia, 2023). Functional foods and medicinal plants can interact with capsaicin and cannabinoid receptors to relieve pain in SCA patients.

A. Interaction with Capsaicin or Vanilloid Receptor (TRPV1) to Relieve Pain

Bioactive compounds in functional foods and medicinal plants interact with transient receptor potential vanilloid channels (TRPV1-TRPV6), a superfamily of 28 ligand-activated ion channels in humans and rodents, to reduce pain sensitivity (Camerino *et al*., 2007; Sadler and Stucky, 2018). Capsaicin-containing compounds initially stimulate TRPV1, causing a warming sensation, but repeated exposure desensitizes the receptor, providing prolonged pain relief (Bley, 2010).

Compounds such as catechins, curcumin and other antioxidants inhibit TRPV channels (Banerjee *et al*., 2019) and reduce oxidative stress and inflammation, thus mitigating pain (Hou *et al*., 2020). Additionally, gingerol in ginger and menthol peppermint modulate TRPV channels to produce analgesic effects (Akin *et al*., 2021).

These interactions make functional foods and medicinal plants valuable for pain management in SCA patients.

B. B. Interaction with Cannabinoid Receptors to Relieve Pain

Cannabinoid-containing functional foods and medicinal plants, such as the psychoactive components of Cannabis sativa (Graham *et al.,* 2009) and β-caryophyllene found in black pepper, cloves, carrots and rosemary, modulate cannabinoid receptor 1 (CB1) in the central nervous system (CNS) and cannabinoid receptor 2 (CB2) in peripheral nerves (Graham *et al.,* 2009; Ameh *et al*., 2012; Anthony *et al*., 2020).

CB2, in particular, has shown promise for pain and inflammation management without the psychoactive effects of CB1 (Atwood and Mackie, 2010). CB2 activation involves binding to Gi protein α-subunit [G(i/o)], which modulates cyclic adenosine monophosphate (cAMP) levels and activates intracellular K^+ channels (Costa *et al*., 2007; Anthony *et al*., 2020).

This CB2-G(i/o) complex triggers the release of gamma-aminobutyric acid (GABA) and glutamate, both involved in pain modulation (Anthony *et al*., 2020). β-caryophyllene's selective activation of CB2 exerts anti-inflammatory effects and reduces neuropathic pain by decreasing pro-inflammatory cytokines, immune cell migration and modulating peripheral pain pathways (Turcotte *et al*., 2016).

The targeting of CB2 by β-caryophyllene offers an alternative for pain relief, reducing reliance on addictive conventional drugs like opioids and minimizing side effects (Anthony *et al.,* 2020).

CONCLUSION

The potential of functional foods and medicinal plants in managing SCA has garnered significant research interests. Their dual capacities to inhibit or reverse RBCs' sickling and relieve pain through interactions with haemoglobin and ion channel receptors represent promising alternatives to conventional therapies.

Studies have shown that targeting the allosteric properties of haemoglobin can induce conformational changes that enhance oxygen affinity and reduce Hb*S*

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polymerization, which is pivotal for preventing or reversing sickling. This evidence supports the role of bioactive compounds in functional foods as complementary interventions for SCA management.

Also, the analgesic properties of these natural agents, achieved through modulation of ion channels and receptors, further underscore their value.

Despite promising findings, challenges remain, such as the bioavailability of active compounds, variability in plant composition, inadequate molecular understanding of antisickling pathways and limited clinical trials.

Addressing these gaps requires standardizing phytochemical profiles, deepening the molecular understanding of antisickling pathways and conducting comprehensive clinical studies to confirm their efficacy in humans. This will help translate the promising *in vitro* and animal model researches into standardized therapeutic protocols.

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