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Reducing Free Radical Potential of *Echinochloa Frumentacea*: A Millet from Uttarakhand Himalayas

Anupam Thakur[1], Neelam Painuly[2*], B Vishnu Vardhan[1], Komal Hangloo[1], Shivam Chandra[1]
[1]Research Scholar, School of Pharmacy and Research, DBUU, Dehradun, Uttarakhand;
anupampharm25@gmail.com
[2*]Associate Professor, School of Pharmacy and Research, DBUU, Dehradun, Uttarakhand
sopr.neelam@dbuu.ac.in
Corresponding Author's Email: (sopr.neelam@dbuu.ac.in)

Abstract: *Oxidative stress is produced by overproduction of free radicals such as reactive oxygen species and reactive nitrogen species, that produces harmful effect by damaging the biomolecules (lipids, proteins and DNA). It decreases the antioxidant defense system of body by increasing the lipid peroxidation and plays a key role in frequent pathological diseases like ageing, cancer, cardiovascular disease, neurological disorders, diabetes & ischemia. The aim of this review is to explore antioxidant potential of Echinochloa frumentacea (Sawa rice) that reduces/neutralize the free radicals. Phytoconstituents present in Sawa rice such as phenolic compounds, flavonoids, amino acids, alkaloids, terpenoids, saponins and fatty acids are responsible for its antioxidant property. Plants that show antioxidant property have been scientifically proven to minimize the impact of free radicals via DPPH assay, superoxide anion, nitric oxide, hydroxyl ion and hydrogen peroxide radical assays. This study concluded that Sawa rice possess high antioxidant activity that neutralizes the free radicals. So, there is a need of pharmacological evaluation of this plant against free radical induced disease/condition and formulation of pharmaceutical compounds.*

Keywords*: Free radicals, Anti-oxidant, Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS).*

INTRODUCTION

In past years, curiosity about the free radicals has increased because they are involved in several diseases and many physiological conditions. There is lot of evidence that biological system has adapted to survive with free radicals & have developed frequent beneficial uses of them in various physiological functions [1,2,3].

Oxygen is very important element for life. Energy produced via electron transport chain when oxygen is utilized by cells, free radicals are formed as a consequence of ATP (adenosine triphosphate) creation by mitochondria [4].

A free radical can be described as "an atom or molecule that are highly reactive because of one or more unpaired electrons present in their molecular orbit" [5,6]. High reactivity of these atoms or molecules make it participate in chemical reaction with all cell components (lipids, proteins & nucleic acids) in the body. By-products of free radicals are generally reactive oxygen species (ROS) & reactive nitrogen species (RNS) [7]. There are four ways in which ROS & RNS can be formed in the cells: [7, 8, 9]

a) **Enzymatic reaction:** produces free radicals that are involved in cytochrome P450 system, phagocytosis, respiratory chain and prostaglandin synthesis.
b) **Non-enzymatic reaction:** reacting oxygen with both organic and ionizing radiation-induced molecules.
c) **Endogenous sources:** mental stress, physiological activities such as intoxication, respiration, fatty acid metabolism and phagocytosis all are responsible for production of free radicals.
d) **Exogenous sources:** alcohol, water & air pollution, cigarette smoke, heavy radiation causes production of free radicals. These exogenous substances are broken down or converted into free radicals once they have entered the body through various pathways.

These ROS and RNS plays both beneficial and harmful role on biological systems. At low level, they employ helpful effects on immune function & cellular responses. At high level, they produce oxidative stress, a destructive process that can harm all cell components including lipids, proteins & DNA [10].

Oxidative stress plays a crucial role in progression of chronic & degenerative diseases such as auto-immune

disorders, cancer, aging, cardiovascular, arthritis and neurodegenerative disorders [11]. Antioxidants are formed by body to fight against oxidative stress, which act as "free radical scavengers" by stopping and fixing damage caused by ROS & RNS. As a result, they can stronger the immune system & lessen the risk of cancer and degenerative disorders [12]. Thus, free radicals play an important role in the pathogenesis of clinical diseases including cardiovascular diseases, neurodegenerative disorders & mutagenesis [13].

Unhealthy food habits and change in lifestyle results to an increase in the amount of clinical human diseases. Synthetic drugs usage has become a key strategy for treating these diseases [14]. The pharmaceutical industry is moving into an era of change due to complications with synthetic drugs, thus the search for new and natural substances is always in the forefront of attention. Phytochemicals are natural compounds produced in plants that developed as potential health benefiting agents [15]. Such compounds can be utilized to treat or control diseases. Researchers have explored at a variety of phytochemical groups and their derivatives in millets that have the potential to control disease [16,17,18].

Echinochloa frumentacea (Sawa rice) is a major millet found in the region of Nepal, China, Japan, Korea and Himalayan region of India for human consumption [19], which is locally known by several names as Jhangora, Oadalu, Sawa rice, Sanwa and Sanwank and belongs to Poaceae family. Key reason for rebuilding interest in Sawa rice are its richness in many nutrients, fullness of dietary fibres, proteins, phytochemicals, and non-nutritive plant protective functional constituents [20,21] that show lots of pharmacological activity like Antidiabetic, Anti-inflammatory, Anti-oxidants, Cardioprotective etc. [22,23].

This review provides full detail about the role of Sawa rice to reduce free radicals in disease, by its phenolic and flavonoid phytochemicals that responsible for its antioxidant property. It is known for its proven antioxidant property via fighting with DPPH free radicals, Superoxide anion, Hydrogen peroxide & various type of oxidative stress induced by free radicals and reducing the risk of chronic diseases & neurodegenerative disorders [24].

ROLE OF FREE RADICALS IN DISEASES

In recent years, interest is increased in understanding the role of free radicals in diseases. A molecule in which one or more unpaired electrons are present in its outer orbit is known as free radicals. Mainly it divided into two species: ROS (reactive oxygen species) & RNS (reactive nitrogen species). Both of these plays double role as helpful & toxic based on their beneficial & deleterious effect on biological systems. At moderate level they show beneficial effects & include in several physiological functions like in immune function, in mitogenic response, in various cellular signaling pathways & in redox regulation [10, 25]. At high level they create oxidative & nitrosative stress, respectively, producing potential harm to the biomolecule including lipids [26], proteins [27] and DNA [28].

Both the stresses are developed when an imbalance occurs between the free radical formation & antioxidant defense. Most importantly, the excessive creation of free radicals, damages the integrity of various biomolecules that leads in various human diseases like rheumatoid arthritis, diabetes mellitus, cancer, neurodegenerative disorders, cataracts, inflammation, cardiovascular diseases, burns, respiratory diseases and in aging process etc [7]. The role of free radicals in main disease conditions (see Fig. 1) is discussed below.

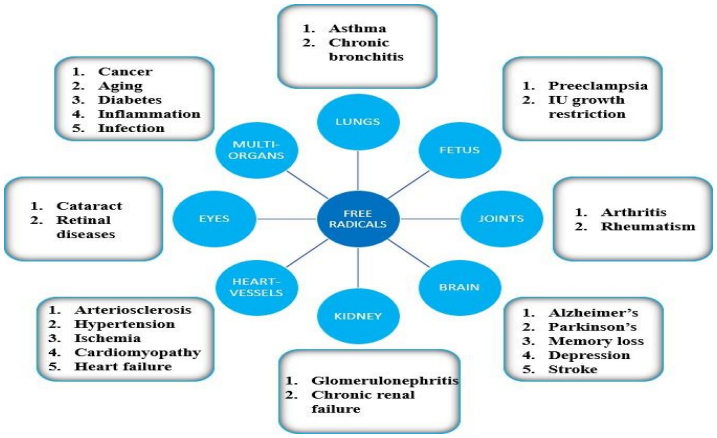

Figure 1: Disease caused by free radicals

Diabetes Mellitus (DM)

Diabetes mellitus is a chronic disorder characterized by enhanced blood glucose levels (hyperglycemia) resulting from low insulin secretion (Type I diabetes), resistance to insulin action (Type II diabetes). .DM is associated with the increased production of free radicals or decreased activity of the antioxidant systems, which leads to development of oxidative stress [29]. The increased glucose levels in DM lead to increased glycolysis that's results in the augmented generation of pyruvate, thus increases the inner mitochondrial membrane potential, followed by mitochondrial dysfunction and increases the production of ROS [30].

Cancer

It is one of the leading causes of death in humans. In comparison with normal cells, cancer cells have higher levels of ROS and are more susceptible to mitochondrial dysfunction due to their higher metabolic rate [31]. Cancer cells display elevated levels of oxidative stress due to activation of oncogenes and loss of tumor suppressors [32]. ROS can damage DNA by inducing base modifications, deletions, strand breakage, chromosomal rearrangements and hyper- and hypo-methylation of DNA [33].

Neurodegenerative Diseases

The central nervous system (CNS) is particularly liable to the oxidants due to the presence of high lipid content, high consumption of oxygen, and low levels of antioxidant enzymes. Hippocampus, substantia nigra, and the striatum are the regions of brain that are liable to attack by free radicals [34,35]. The oxidative stress state has been also implicated in several neurodegenerative diseases such as Alzheimer's [36], Parkinson's [37], Huntington's, lateral amyotrophic sclerosis [38], and multiple Sclerosis [39].

Cataract

It is the most common cause of the visual impairment affecting about 25 million people throughout the world, with the highest incidence occurring in developing countries [40]. Although a number of factors such as genetic factors, diabetes, aging, smoking, drugs, malnutrition, radiation (x rays and UV rays) and alteration in both endocrine and enzymatic equilibrium have been implicated in cataract formation, the free radical induced oxidative stress is considered as one of the major underlying mechanisms of cataract disorder [41]. It has been confirmed that oxidative stress causes lens opacification in both cultured lens systems and experimental animal models [42].

Cardiovascular Diseases

Cardiovascular diseases are a group of diseases that affect the heart & blood vessels, including veins, capillaries and arteries. 40% of adults globally suffer from hypertension (HT), a serious health issue [43]. Hypertensive individuals are more likely to suffer from heart disease, stroke, kidney damage, and early death. Hypertension results from reduced endothelium-dependent vasodilation caused by increased ROS production, which removes NO• by generating ONOO- [44].

Understanding the role of free radicals in numerous diseases has opened up avenues for therapeutic interventions, especially through antioxidants, lifestyle changes and targeted drug development. Therefore, maintaining a balance between free radicals & antioxidants defence is crucial for health and disease prevention.

ANTIOXIDANT MECHANISM

More attention has been received than ever before to the problems of oxidative stress and how antioxidants could prevent it. Our natural defenses against damage by free radicals are antioxidants or free radical scavengers. Antioxidants can be formed endogenously (superoxide dismutase (SOD) & reduced glutathione (GSH)) as well as exogenously, usually through diet (vit C & vit E) [45, 46]. Antioxidants have the ability to neutralize the extreme of free radicals that produced during metabolic processes, such as those that protect the gut from inflammation and injury [47, 48], shield cells from their toxic effects, and helps in disease prevention.

Mainly three primary mechanisms for the antioxidant activity are chain breaking, preventive and synergetic [49].

Chain breaking mechanism: In this step mainly vitamins, non-protein endogenous antioxidants and flavonoids inhibit the oxidation processes by scavenging free radicals. The chain breaking antioxidant AH

scavenges the peroxyl radical LOO˚, inhibit the propagation reaction and form less reactive antioxidant radical so that no further reaction will occur with lipids as shown in below equation:

$$LOO^{\circ} + AH \longrightarrow LOOH + A^{\circ}$$
$$A^{\circ} + LOO^{\circ} \longrightarrow AOOL$$

Preventive: (see fig. 2)

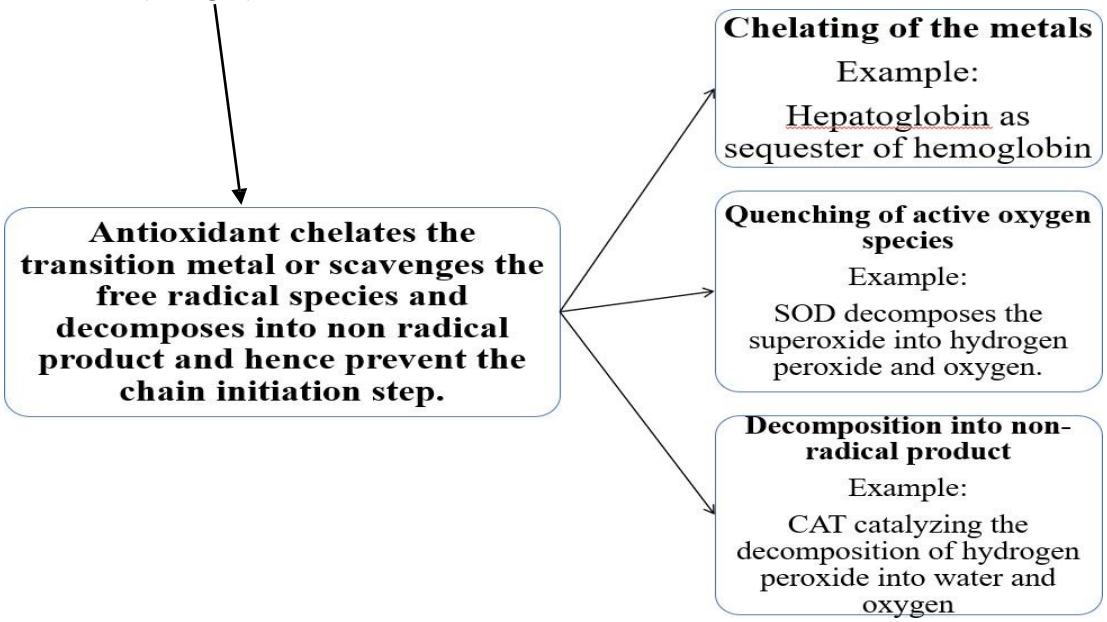

Figure 2: Preventive mechanism of antioxidant.

Synergetic: It works as- one antioxidant couple with another and work in synergy. Together they are more effective than the single antioxidant alone. For example: when tocopherol is used in combination with citric acid, marked synergistic effect has been observed because of the chain breaking ability of tocopherol and metal chelating activity of citric acid.

ECHINOCHLOA FRUMENTACEA

Globally, *Echinochloa frumentacea* (Sawa rice) is largely produced in India mainly in Uttarakhand Himalayas, both in terms of area (0.146Mha) & production (0.147MT) with the average productivity of 1034kg/ha [50]. It is one of the oldest millet that are mainly used in Asian countries and belongs to Poaceae family, with several names as Jhangora, Sawa rice, Shyama rice, Vrat ke Chawal, Shamyak, Indian barnyard millet, Billion-dollar grass etc. It is an excellent choice for diabetics, expectant mothers and infants as a healthy diet. In recent years, experts have become increasingly interested in its potential health advantages [51].

Botanical description: [52]

Figure 3: *Echinochloa frumentacea* plant

Plant Height: 180 - 220cm (4-6feet)
Seeds: Small and spherical in shape (3-4mm); Pale yellow and brown color
Stem: Hollow slender, erect and slightly reddish color
Leaf: Long, narrow and glabrous leaves (30-60cm length and 1-3cm width) **Root:** Fibrous and shallow roots
Inflorescence: Panicle (open branch cluster of flowers; 30-45cm)
Sawa rice is mostly grown in the kharif season in the hilly regions of Uttarakhand Himalayas, up to 2300m above sea level [53]. Among all the millets, it grows one of the fastest, achieving maturity in 45 days when planted under ideal atmospheric conditions [54]. It's a comfortable zone crop and can withstand low to moderate rainfall (500 to 700mm) [55]. Its leaves encircling the stem and its roots penetrate deeper into the soil that helps the plant withstand periods of drought by accessing water from lower soil layers. The roots also aid in soil stabilization and prevent erosion [56].

Nutritional and Phytochemical profile

Sawa rice are a natural nutraceutical food, especially for people at high risk for non-infectious diseases like diabetes, heart disease, obesity, and cancer [53] because of fair source of protein which is highly digestible, carbohydrates, fat, micronutrients (mainly iron, magnesium, calcium and phosphorus) and are excellent source of dietary fibres per 100g are shown in Table 1 [16, 22].

Table 1: Nutritional value of Sawa rice per 100g

NUTRITION	**VALUE**
Calories	350-400 kcal
Carbohydrates	68.8%
Crude fibre	6.7%
Fat	3.9%
Protein	10.1%
Moisture	8.74%
Insoluble dietary fibre	8.4%
Soluble dietary fibre	4.2%
Total dietary fibre	12.5%
Total minerals	2.1%
Iron	5mg
Calcium	19mg
Magnesium	83mg
Phosphorus	281mg

In addition to its nutritional value, this millet's bioactive phytochemicals may have health-beneficial effects in lowering the risk of several oxidative stress-mediated diseases [57] because of antioxidant, anti-inflammatory, anticarcinogenic, antimicrobial, antidiarrheal, antiulcer and anti-cardiovascular properties [58, 59].

Natural compounds produced by plants that have the potential to improve health are known as phytochemicals [60]. These compounds are utilized as agents to treat or control diseases. Sawa rice contains several phytochemicals includes flavonoids, phenolic compounds, alkaloids, tannins, terpenoids, saponins, amino acids, vitamin C and E [61, 62] that shows notable pharmacological properties. Phytoconstituents present in Sawa rice with their pharmacological properties is discussed below:

Phenolic compounds: Phthalic acid, Hexadecanoic acid, Sitosterol, Campesterol, Catechin, Lupeol, (Quercetin-3-O-galoctoside), Ascorbic acid, Gallic acid, (9,12-octadecadienoic acid), Ferulic acid etc. are present in Sawa rice that show promising anticancer, antioxidant, anti-inflammatory, reducing free radicals, antimicrobial properties [63].

Flavonoids: Orientin, Iso-orientin, Vitexin, Iso-vitexin, Kaempferol, Myricetin, Luteolin, Apigenin are the compounds present in Sawa rice that shows Anticancer, Antioxidant, Cardioprotective, having free radical reducing potential, neuroprotective etc. properties [64].

Terpenoids: Triterpenoids such as γ-sitosterol, stigmasterol and Sterol terpenoid (Ergosterol) are present with Antitumor and Anti-HIV properties [63].

Amino acids: Alanine, cystine, arginine, glycine, histidine, tryptophan, leucine, proline, threonine, tyrosine, serine, valine etc. compounds are present in Sawa rice with notable Anti-inflammatory, Antioxidant, Antimicrobial, Anti-cancer etc. properties [65].

Fatty acids: Arachidic acid, linoleic acid, ecosenoic acid, caprylic acid, stearic acid, palmitic acid, myristic acid etc. are present and shows cardioprotective, antidiabetic, neuroprotective etc. properties [66].

Some Antinutrients (Phytic acid, Oxalic acid and Tannic acid), Vitamins (Thiamine Riboflavin, Ascorbic acid/Vit. C, Pantothenic acid, Folic acid, Niacin, Vit. E as α-Tocopherol & γ-Tocopherol), alkaloids, tannins, steroids and saponins are also present in *Echinochloa frumentacea* [66]. Having good nutritional and pharmacological activities, Sawa rice has persisted as a mostly unnoticed millet. Throughout the last decades, very few attempts have been made to investigate the phytochemical analysis and benefits of this millet. Hence more concerted research efforts are essential to evaluate more about phytochemicals and its pharmacological benefits of this millet.

PHARMACOLOGICAL ACTIVITIES

Sawa rice shows notable pharmacological properties because of its phytoconstituents. Properties are:

1) Anti-nutritional [67]
2) Immunostimulatory [68]
3) Anti-oxidant and Hepatoprotective [69]
4) Hydrogen peroxide-Scavenging Enzyme [70]
5) Anti-inflammatory [71]
6) Hypoglycemic and Hypolipidemic [72]
7) Cytotoxicity and Antibacterial [65].

ANTIOXIDANT STUDIES AN EVIDENCE

Antioxidants are the natural defense system of human/plant, also known as free radical scavengers that helps in prevention of various diseases caused by extreme formation of free radicals. The antioxidant property of Sawa rice is determined by various methods as follows:

Calculating the total phenolic and flavonoid content: *Vanapatla* et al., 2017 [69], used Aluminum chloride & Folin Ciocalteu reagent assay methods to determine the total flavonoid & phenolic contents in methanolic extract of Sawa rice extract. They carried out triplicate of total flavonoid & phenolic content & stated it as rutin equivalents (RE) & Gallic acid equivalents (GAE) in mg/g. Phenolic & flavonoid content plays an important role in concluding the oxidative stress formed by free radicals[73].

Results: The total phenolic & flavonoid contents of methanolic extract of Sawa rice were calculated as 138.53±2.11mg & 7.56±1.29mg of GAE & RE equivalents per gram of extract.

Determination of antioxidant activity of Sawa rice by different assays: *Vanapatla* et al., 2017 [69], calculates IC50 value of methanolic extract of Sawa rice with comparing standard (rutin/ascorbic acid) to assess its antioxidant property via following assays:

DPPH free radical scavenging assay: It is one of most commonly used method to evaluate the antioxidant activity. 2,2-diphenyl-1-picrylhydrazyl (DPPH) is a free radical that appears deep violet color; after accepting a hydrogen atom from antioxidants it becomes reduced and solution changes from violet to yellow.

Superoxide anion assay: This assay scavenges the superoxide anion ($O_2^{\cdot-}$) radical with presence of antioxidant.

Nitric oxide assay: This assay measures the ability of extract to scavenge nitric oxide (NO) radical, which are reactive nitrogen species involved in inflammation and cellular damage.

Hydroxyl ion assay: This assay evaluates the ability of extract to neutralize hydroxyl radical (˙OH), which among the most damaging ROS.

Hydrogen peroxide assay: Determines the capacity of extract to scavenge hydrogen peroxide, a non-radical ROS that can form hydroxyl radicals in vivo.

Reducing power assay: This assay measures the electron-donating ability of an antioxidant, indicating its potential to reduce oxidants (like Fe^{3+} to Fe^{2+}).

Table 2: The result of IC50 values of methanolic extract of Sawa rice and standard against these assays.

Free radical Assays	IC50 value of methanolic extract of Sawa rice in µg/mL	IC50 value of standard in µg/mL
DPPH free radical scavenging assay	51.49 ± 1.8	0.39 ± 0.12 (Rutin)
Superoxide anion assay	589.67 ± 7.7	0.34 ± 0.06 (Rutin)
Nitric oxide radical assay	47.89 ± 3.9	6.14 ± 0.24 (Ascorbic acid)
Hydroxyl ion radical assay	450.21 ± 5.1	3.12 ± 0.12 (Mannitol)
Hydrogen peroxide radical assay	410.8 ± 3.25	3.18 ± 0.05 (Ascorbic acid)

The reducing power of the methanolic extract derived from Sawa rice is quantified in ascorbic acid equivalents, yielding a measurement of 25.13±1.91mg.

This result shown by *Vanapatla* et al., 2017 [69] proves the antioxidant potential and reducing free radicals' ability of *Echinochloa frumentacea* (Sawa rice), that helps in prevention of various diseases caused by extreme production of free radicals.

CONCLUSION

When an imbalance occurs between antioxidants & oxidants, free radicals are produced and participate in many pathological and physiological conditions by damaging lipids, proteins & nucleic acids, that contributes in number of diseases including diabetes mellitus, cancer, rheumatoid arthritis, cardiovascular disease, neurodegenerative disorders, cataracts, asthma, etc. Antioxidants play crucial role in reducing such effect of free radicals in various disease. *Echinochloa frumentacea* (Sawa rice) stands out as a valuable source of antioxidants with significant potential for reducing free radicals and oxidative stress due to their flavonoids

and phenolic compounds present in it. Phytochemicals present in it are not only supports health but also offers therapeutic benefits against various diseases like inflammation, microbial infection, cardiovascular disease, diabetes mellitus etc. But exact information about its phytochemicals and their mechanism of action are not yet explored. So, in future formulation based on this millet may be helpful in various disease caused by free radicals such as Type-II diabetes mellitus, neurodegenerative disorders, cancer, rheumatoid arthritis, cardiovascular diseases, cataracts, wound healing, asthma, aging etc.

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