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Review Article

Tempe as superior functional antioxidant food: From biomechanism to future development of soybean-based functional food

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Abstract

Foods that have nutritional value along with additional health advantages are referred to as functional foods. Fruits, vegetables, and spices are rich sources of antioxidants, which can help prevent damage from free radicals and environmental stress. It has been demonstrated that consuming foods high in antioxidants lowers the risk of degenerative diseases such as cancer, emphysema, immunological deficiencies, respiratory disorders, heart disease, and stroke. It also lowers the risk of Parkinson's disease and other inflammatory conditions. Traditional Indonesian fermented soybean-based food products, or soybeans and known as "tempe", have been associated with a host of health benefits, including a lower risk of cardiovascular disease, a lower risk of cancer, improved bone health, and enhanced immunological function. This article investigates tempe's potential as a meal with antioxidant properties and suggests a mechanism via which it can trigger the Nrf2-mediated antioxidant response. The study offers insights into the potential applications, development, and potentiation of tempe by synthesizing potential biomolecular pathways for its antioxidant actions at the cellular level.

Keywords

fermented food, functional food, Nrf2-mediated antioxidant response, oxidative stress, soybean

Introduction

The term “functional food” refers to food that provides health-related benefits in addition to its nutritional interests (Granato et al. 2020). Foods that are rich in antioxidants are considered functional foods owing to the beneficial properties of antioxidants towards human health (Wilson et al. 2017). Antioxidants can intercept or slow down the damage cells get from free radicals, unstable particles that the body produces when it reacts to certain types of environmental pressures, and others such as stress, inflammation, and exposure to UV and air pollution (Gulcin 2020). Naturally, antioxidants are abundantly present in a myriad of food sources, particularly fruits, vegetables, and spices. Some well-known examples of natural antioxidants include vitamin C (ascorbic acid), vitamin E (tocopherol), beta-carotene, and polyphenol (Santos-Sanchez et al. 2019). Consumption of foods rich in antioxidants has been scientifically proven to reduce and limit the risk of degenerative diseases, including heart disease, cancer, arthritis, stroke, respiratory diseases, emphysema, immune deficiency, Parkinson’s disease, and other inflammatory or ischemic conditions (Zhang et al. 2015).

Consuming soybean (*Glycine max*), either fermented or unfermented, has been a typical characteristic of food culture in many Asian countries (Rizzo and Baroni 2018). Although soybeans are mainly consumed in Asia, the trend of soybean consumption in western countries is continuously increasing in accordance with the popularity of the vegetarian diet and the widespread perception of soybeans as healthy food (Nair et al. 2023). Indeed, the consumption of soybean-based food products has been linked to many health benefits, including reduced risk of cardiovascular diseases and cancer, prevention of gynecological problems in women, better bone health in the elderly, and immune potentiation (Mani and Ming 2017).

Tempe is a traditional fermented soybean-based food product from Indonesia (Ahnan-Winarno et al. 2021). It has been an integral part of Indonesian food culture for hundreds of years (Romulo and Surya 2021). The fermentation of tempe involves *Rhizopus* spp. which forms white mycelia covering and binding soybean grains together to form a compact cake. Tempe is widely accepted as highly nutritional and healthy food rich in protein and is even often addressed as a “vegan meat” (Ahnan-Winarno et al. 2021). A 100 g of fresh soybean tempe contains 20.8 g protein, 13.5 g carbohydrate, 8.8 g fat, and a considerable amount of potassium (234 mg) (Romulo and Surya 2021). Tempe has been proposed to be a functional food and the functionality of tempe is suggested to be associated with the presence of bioactive compounds with antioxidant activities known as isoflavones (Nout and Kiers 2004).

This article aims to explore the potential of tempe as an antioxidant-functional food. Based on recent literature, we propose a mechanism by which tempe may exert antioxidant activities by activating the Nrf2-mediated antioxidant response. The novelty of this article is focused on providing a holistic approach regarding the role of tempe in modulating cellular antioxidant response, a topic that has been very little evoked in any previous studies. This article synthesizes the possible biomolecular mechanisms for the antioxidant activities of tempe at the cellular level, which have never been reported before. Finally, we also provide some insights into the further development, application, and potentiation of tempe as an antioxidant functional food.

Tempe as an antioxidant functional food

Fermenting soybeans into tempe has many nutritional interests. Fungal activities allow the degradation of anti-nutritional compounds naturally present in soybean (such as anti-trypsin and phytic acid) and the hydrolysis of proteins into shorter polypeptides, thus improving the bioavailability of proteins and other nutrients (Handoyo and Morita 2006). The formation of free amino acids during fermentation gives tempe a unique and distinctive flavor, particularly the umami taste resulting from glutamic acid (Amin et al. 2020). Bioactive peptides synthesized during tempe fermentation have been reported to exert anti- hypertensive, anti-diabetic, antioxidant, and anticancer activities (Sanjukta and Rai 2016). Vitamin B12, which is the most critical nutrient in vegan diets and not present in soybeans, is formed during the fermentation of tempe by the bacteria *Citrobacter freundii* or *Klebsiella pneumoniae* (Kustyawati et al. 2020). Recent studies have also shown that tempe also contains probiotics that are suggested to be beneficial towards gut health by maintaining the composition of beneficial gut microbiota (Handajani et al. 2022). In addition, tempe is also suggested to be an excellent source of paraprobiotics that are defined as inactivated or non-viable microbial cells conferring health benefits (Stephanie et al. 2017). A study showed that the presence of non-viable microorganisms in cooked tempe triggered immune responses (mucosal IgA) in the intestine of rats (Soka et al. 2015).

Tempe is a potential source of antioxidants. Tempe flour-based products contain a higher level of flavonoids compared to wheat flour-based products (Bintari et al.

2020). Tempe-based soygurt (a yogurt-like fermented drink made from tempe aqueous extract) was reported to contain more antioxidants and protein compared to plain yogurt made from cow milk (Bintari and Parman 2019). Soybean is a distinctive dietary source of isoflavones. In soybean, isoflavones are mainly bound to sugar molecules and, therefore, are called isoflavones glycosides. During the fermentation of tempe, *Rhizopus* spp. produces the enzyme beta- glucosidase that hydrolyzes isoflavones glycosides into isoflavones aglycones that are not bound to sugar molecules (Da Silva et al. 2011). Genistein, daidzein, and glycitein are the three major isoflavone aglycones present in tempe (Da Silva et al. 2011). Isoflavone aglycones possess a higher bioavailability in humans and exert a stronger antioxidant activity compared to isoflavone glycosides (Lee et al. 2005; Kim and Kim 2020), therefore, tempe can be considered a better antioxidant source compared to unfermented soybeans. Indeed, antioxidant activity was found to be higher in tempe extract than in soybean extract (Surya and Romulo 2020a, 2020b; Lo et al. 2022). In addition, 3- hydroxyanthranilic acid (3HAA) resulting from the fungal metabolism of the amino acid tryptophan has also been identified as an antioxidant molecule present uniquely in tempe and not in unfermented soybeans (Esaki et al. 1996). 3HAA was previously reported to exert antioxidant properties and induce apoptosis in a human carcinoma cell line (Matsuo et al. 1997).

Nrf2-mediated antioxidant response and food components as its activators

The Nrf2-mediated signaling pathway is an essential cellular defense mechanism against oxidative and/or electrophilic stresses (Shaw and Chattopadhyay 2020). Such a pathway is closely associated with cardiovascular diseases, neurodegenerative diseases, cancer, and aging in humans (Shaw and Chattopadhyay 2020). Nrf2 (nuclear factor erythroid 2-related factor 2) is a ubiquitous transcription factor that directs various transcriptional programs in response to cellular stress signals. Nrf2 is primarily regulated by Keap1 (Kelch-like ECH-associated protein 1) that binds directly to Nrf2 and acts as its inhibitor. Under basal conditions, Nrf2 is continuously degraded by the ubiquitination system in the cytoplasm. However, in response to oxidative stress, Nrf2 is released from Keap1, translocates into the nucleus, and acts as a transcription regulator for gene expression. In the nucleus, Nrf2 binds to ARE (antioxidant response element), a sequence in the promoter regions of a wide variety of genes involved in antioxidant response and cytoprotection (Tonelli et al. 2018). Some of the well-known genes whose expression is mediated by Nrf2 are the cellular antioxidant and detoxification enzymes, including catalase, glutathione peroxidase, glutathione reductase, superoxide dismutase, peroxiredoxin, and NAD(P)H quinone dehydrogenase (Saha et al. 2020).

In addition to oxidative stress, a diverse array of stimuli can activate the Nrf2-dependent antioxidant response. Interestingly, many food components, particularly those with antioxidant activities, can activate Nrf2 by interacting with Keap1 and modifying its residues (mainly Cys-151), allowing the liberation and activation of Nrf2 to the nucleus (Paunkov et al. 2019). Several antioxidants with strong antioxidant activities that have been shown to act as Nrf2 activators include sulforaphane (from broccoli), resveratrol (from grapes), quercetin (from onions), curcumin (from turmeric spice), catechin (from green tea), and other antioxidants found in other natural sources (Paunkov et al. 2019).

Discussion

There are several studies that show in vivo, in vitro clinical evidence of Tempe consumption, on lung health, cancer, liver, skeletal muscle recovery, anemia, bone health, malnutrition, gut health, obesity, type 2 diabetes mellitus, cardiovascular health, and Alzheimer's disease (Ahnan-Winarno et al. 2021).

Fig. 1 recapitulates the proposed mechanism of tempe as an antioxidant food. Fungal fermentation allows the conversion of isoflavone glycosides to isoflavone aglycones with a higher bioavailability and antioxidant activity (Lee at al. 2005; Kim and Kim 2020). Isoflavones were also previously reported to be an Nrf2 activator (Li and Zhang 2017; Liang et al. 2019). Isoflavones are suggested to interact with the cysteine residues of Keap1, leading to the activation of Nrf2 and the promotion of gene expression. With their antioxidant activity, isoflavones can also directly tackle oxidative stress by neutralizing reactive oxygen species (ROS). Furthermore, isoflavones are also suggested to activate Nrf2 by inhibiting the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway known to negatively regulate Nrf2 activity (Ahmad et al. 2013; Kaushik et al. 2018). All these proposed pathways lead to the activation of Nrf2 mediated by isoflavones.

3HAA is another antioxidant molecule derived from tryptophan during the fermentation of tempe (Esaki et al. 1996). In *Caenorhabditis elegans*, an animal model for *in vivo* studies on aging, 3HAA has been shown to increase resistance to oxidative stress during aging by directly degrading hydrogen peroxide and activating the antioxidant response mediated by skinhead-1 (SKN-1), the ortholog of human Nrf2 in *C. elegans* (Tullet et al. 2017). According to these findings, we suggest that 3HAA could also be able to induce the Nrf2-mediated antioxidant response in humans. In addition, 3HAA is also able to directly counterbalance oxidative stress owing to its antioxidant activity.

In recent studies, tempe was demonstrated to improve cellular antioxidant status and induce the expression of cellular antioxidant enzymes, including catalase and superoxide dismutases (SOD1, SOD2, and SOD3) in different cellular models (Ahmad et al. 2021; Surya et al. 2021). These enzymes are expressed by Nrf2 target genes, thus

Table 1. Health benefits of Soy-based Tempe.

Health outcomes	Authors	Publication date	Key findings
Lung Health	Setiawan et al.	2016	Finds that soy-based supplements particularly tempeh illustrate effectiveness on Tuberculosis patients who are on antimicrobial therapy.
Cancer	Nurkolis et al.	2022	Tempeh contains bioactive chemicals that function as anticancer agents inhibiting cell proliferation and angiogenesis, also works as an antioxidant, and induces apoptosis of cancer cells.
Liver	Reggie et al.	2020	The study showed that the expression of cellular antioxidant enzymes, such as superoxide and catalase dismutases, in HepG2 cells, could be boosted. Thus, tempeh might be found to have the ability to protect liver cells, by strengthening their antioxidant resistance
Skeletal Muscle Recovery	Gomes et al.	2021	This study illustrates that fermented soybean antioxidant activity reduces oxidative stress in skeletal muscle and improves performance when undergoing high-intensity exercises in rats, indirectly promoting a healthier muscle environment for the repair and regeneration process.
Anemia	Sudargo et al.	2013	The study concludes that the bioavailability of iron in iron-fortified tempeh is increased.
Obesity	Watti et al.	2020	Suggests that tempeh consumption at the amount of 150 grams a day for 28 days can practically reduce high-sensitivity C-reactive protein and increase levels of HDL cholesterol.
Type 2 Diabetes Mellitus	Park et al.	2010	Fermented soybean has shown possible advantages for patients with type 2 diabetes, including reduced insulin resistance, improvement of glucose control, and delay or prevention of disease progression.
Cardiovascular Health	Barus et al.	2019	Significant attention is given to soybean-containing foods because of their potential capacity for lowering the emergence and progression of many chronic diseases such as osteoporosis, cancer, Alzheimer's disease, cardiovascular disease, and stroke.
Alzheimer's disease	Subali et al.	2022	Without the use of medication, tempeh can provide Alzheimer's patients with the nutrition they require to naturally enhance their condition and overall health.

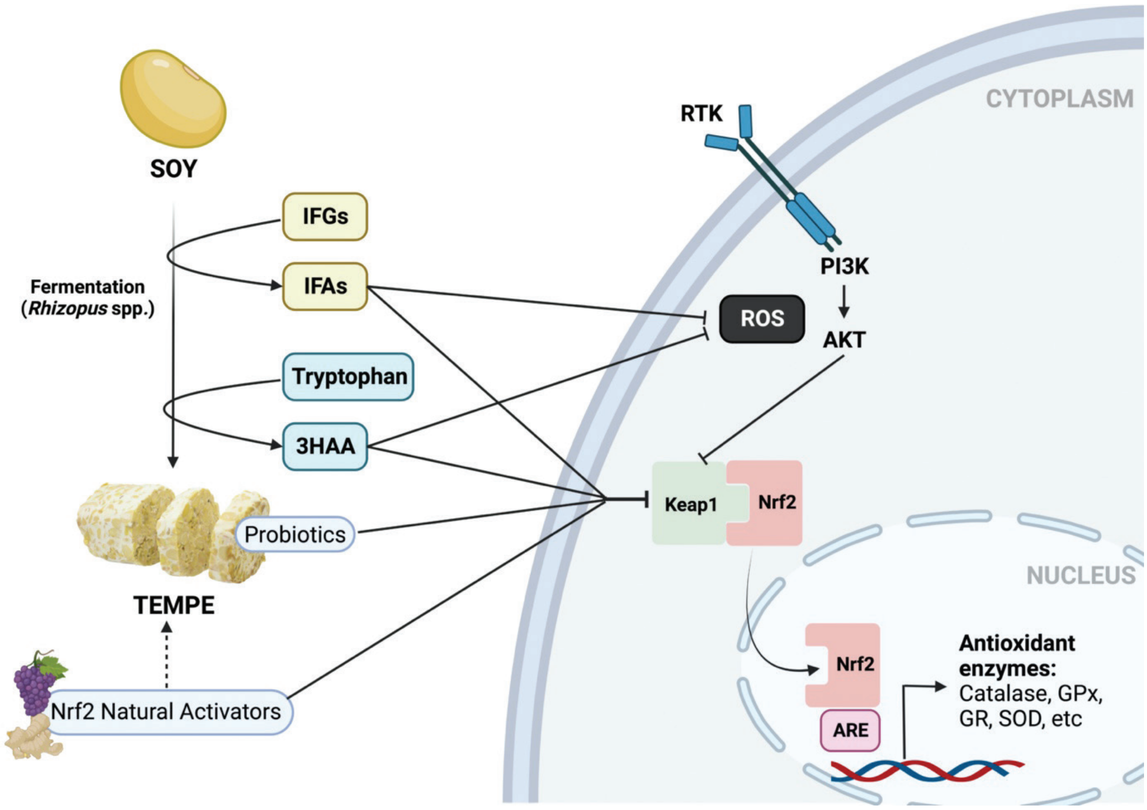

Figure 1. Proposed-biomechanism of tempe on the modulation of cellular antioxidant status *via* the Nrf2- dependent signaling pathway. Abbreviations: 3HAA: 3-hydroxyanthranilic acid; AKT: protein kinase B; ARE: antioxidant response element; GPx: glutathione peroxidase; GR: glutathione reductase; IFAs: isoflavone aglycones; IFGs: isoflavone glycosides; Keap1: Kelch-like ECH-associated protein 1; Nrf2: nuclear factor erythroid 2-related factor 2; PI3K: phosphoinositide 3-kinase; ROS: reactive oxygen species; RTK: receptor tyrosine kinase; SOD: superoxide dismutase.

suggesting that Nrf2 is likely to be involved in the expression up-regulation of cellular antioxidant enzymes by antioxidants in tempe (Tullet et al. 2017).

Since tempe contains both probiotics and their nutrients generally known as prebiotics (fiber and other polysaccharides), tempe can be suggested to be a synbiotic food (Ahmad et al. 2021). Therefore, the consumption of tempe could modify and balance the composition of gut microbiome (Soka et al. 2014). Gut-resident probiotics synthesize a plethora of metabolites that may be reabsorbed in the intestine and alter the cellular antioxidant status via the Nrf2-mediated pathway (Sadovnikova et al. 2021). In previous studies, the consumption of probiotics has been linked to the activation of Nrf2 in different tissues that led to protection against oxidative liver injury, lung injury, and cardiovascular diseases (Saeedi et al. 2020; Aboulgheit et al. 2021; Song et al. 2021).

To potentiate the antioxidant activity of tempe, we also propose the combination of tempe with other ingredients that are known as Nrf2 activators, in particular spices with bioactive compounds (Zhang and Chapman 2020). Such a combination would strengthen the Nrf2-mediated antioxidant response, leading to a better cellular antioxidant status and a higher expression of cytoprotective enzymes. In a recent study, applying probiotics in tempe production was also shown to increase the antioxidant activity of tempe (Lo et al. 2018).

In addition to having a promising potential as an antioxidant food, tempe also has the potential to be developed into an innovative healthy meal (Nurkolis et al. 2022). Tempe can be used as a mixed food ingredient (MFI). Tempe flour has been supplemented with eel flour or algae to increase its antioxidant activity (Nurkolis et al. 2021; Ngadiarti et al. 2022). Tempe essence has been used as a breast milk complementary to instant porridge for infants (Sukardi et al. 2021). Tempe has also been added to different kinds of food products, including cream soup, cereal bars, and nuggets (de Melo et al. 2020; Setiawan et al. 2021; Suriani et al. 2021).

Taken together, we suggest the development of tempe as an antioxidant functional food based on the literature-based proposed mechanism. Such a development could support the potential of tempe in disease prevention, such as cancer and cardiovascular diseases. We propose that the future perspectives of tempe application as an antioxidant functional food should be articulated around integrating tempe into daily consumed foods and developing innovative tempe-based food products. Identification of different metabolites in tempe through foodomics or metabolomics would also be essential to perform to further explore the health-promoting compounds present in tempe.

Conclusion

Tempe is thought to be a superior source of antioxidants than unfermented soybeans. In fact, it was discovered that tempe extract has greater antioxidant activity than soybean extract. This article explores the possibility of tempe as an antioxidant-rich meal and proposes a method by which tempe may activate the Nrf2-mediated antioxidant response, which have never been reported before. The research synthesizes possible biomolecular routes for tempe's antioxidant effects at the cellular level, providing insights into the prospective applications, development, and potentiation of tempe.

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Not Applicable or Authors declare that this study is review type article, so there are no experiments in animals or humans that need to be declared.

There is no data related to this opinion article, the data were only sourced from the literature listed in this article.

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