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Mediterranean Journal of Chemistry **2024**, 14(1), 33-41

Singgang as a potential antioxidant and anticancer dish: a review

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Abstract: Singgang is one of the popular dishes in Terengganu, Malaysia, that includes fish such as either chub mackerel or Indian mackerel and selected herbs and spices like turmeric, galangal, garlic, sour plum, and chilies. In Asia, these chosen spices and herbs are traditionally defined as any part of a plant that is used in a diet for its aromatic and flavor-enhancing properties. These herbs and spices have highlighted various health benefits to consumers, such as antioxidant, antibacterial, anti-inflammatory, antiproliferative, anticancer, and hypolipidemic. Besides the potential of the singgang dish as a nutritional dish, it was believed that the mixture of fish and selected herbs and spices could synergistically have a positive effect during the cooking process. Herbs and spices have been identified as sources of various phytochemicals, many of which have potential antioxidant activity and have a role in antioxidant defense and redox signaling. In addition, herbs and spices have been identified as anticancers because of their ability to influence the activity of some biomarkers and therefore influence carcinogenic bioactivation. In this review, the roles of selected spices and herbs as antioxidants and anticancer will be discussed, supporting the prospective of the singgang dish as a promising therapeutic mark for future study.

Keywords: Antioxidant; Anticancer; Potential; Singgang; Terengganu.

1. Introduction

Singgang is one of the signature and traditional dishes in Terengganu, Malaysia; that is made by boiling the mackerel fish (chub mackerel or Indian mackerel) with selected herbs and spices such as turmeric, galangal, garlic, chilies, and sour plum [1]. The selected herbs and spices as ingredients have various proven in-vitro and in-vivo health benefits. Turmeric is known to have antioxidant, antibacterial, anti-inflammatory, anticancer activity [2], and galangal has antioxidant, anticancer, anti-inflammatory, anti-fungal, and anti-diabetic [3]. Garlic has been reported to have antioxidant, anti-carcinogenic, and hypolipidemic effects [4]. In contrast, sour plum has antiproliferative, antioxidant, anti-inflammatory, and anti-hyperlipidemia [5] properties, and chilies have anticancer, antioxidant, anti-hypertension, and hypolipidemic effects [6].

A more profound investigation of the singgang dish as a potential antioxidant and anticancer dish has not yet been studied. However, there is supportive evidence from the growing number of studies assessing the selected herbs and spices used in the dish through various pathway diseases such as NRF2 activation [7], LPx and PPx [8], mitochondrial-dependent intrinsic apoptotic [9], Akt/p70S6K [10], PKA, Wnt/γ-catenin, ROS/JNK, and p-AKT/mTOR pathways. It was believed that the mixture of fish, herbs, and spices could become one of the nutritious meals high in antioxidants and unsaturated fatty acids and highly susceptible to LPx and PPx [11].

Previous studies have investigated the phenolic content and antioxidant abilities of spices and herbs, as well as the phenolic content and antioxidant abilities of several cooked fish dishes, spices, and herbs [12-14]. Therefore, we aim to highlight the reported roles of each ingredient used in the singgang dish and its antioxidant capacity and progress towards cancer hallmarks on potential singgang dish such as 1) induced biochemical alterations, LPx and PPx; 2) decreasing pro-survival COX-2 and Cyclin D1; 3) triggered pro-survival autophagy through ROS/JNK and p-AKT/mTOR signaling; and 4) suppressing MMP-9 expression and inhibiting metastasized cancer cell [8, 15-17].

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DOI: http://dx.doi.org/10.13171/mjc02401261761khalil_rohin

Received October 2, 2023
Accepted January 6, 2024
Published January 26, 2024

2. Singgang and antioxidant

Based on Halliwell & Gutteridge [18], an antioxidant is any matter existing at a low concentration compared to those of an oxidizable substrate, which significantly delays or inhibits the oxidation process of that substrate. Mainly, antioxidants in oxidative stress conditions are ROS and RNS scavengers, which involve natural radical and non-radical compounds [19-20]. The exogenous plant antioxidants have been in a great deal of researchers' attention as the progression of cardiovascular and other life-threatening diseases is significantly caused by oxidative stress, the accumulation of oxygen-reactive species in the body [21-22]. Nevertheless, a favorable body defense for countering undesirable effects of oxidative stress can effectively be achieved by supplementation with either exogenous antioxidants or boosting with endogenous antioxidants [23].

The potential of the singgang dish as an antioxidant has previously been reported using 2, 2-Diphenyl-1-picrylhydrazyl (DPPH) and total antioxidant capacity (TAC) assays. Anwar et al., [24] demonstrated that the singgang dish with chub mackerel fish yielded the best antioxidant capacity with higher DPPH and TAC values than the singgang dish with Indian mackerel fish. The researchers suggested that the results depend on the cooking process as heat induces chemical changes in each of the ingredients and fish used in singgang dish that may lead to the breakdown of certain compounds, eventually benefiting the total phenolic content and antioxidant capacity [13,24-25]. Previous studies' preliminary data provides insights into the role of the singgang dish as a potential antioxidant dish.

The role of each spice and herb used in the singgang dish has been reported in several study models, for example, the involvement of turmeric in the direct scavenging of oxygen radicals [7], capsaicin in the inhibition of LPx and PPx [8], and others (Table 1).

Table 1. Studies on herbs and spices of singgang dish ingredients as an antioxidant activity.

Herbs	Authors (year)	Possible role and mechanism proposed
Garlic *(Allium sativum L., Alliaceae)*	Bozin et al., [30]	Garlic extract observed various levels of phenolics (0.05–0.98 mg gallic acid Eq) and flavonoid aglycones (4.16–6.99 mg quercetin Eq) as bioactive compounds.
	Gao et al., [26]	Garlic protein and its hydrolyzed GHP-P and GPH-T proposed significant and anti-hypertensive effects towards H_20_2-induced oxidative damage by inhibiting the ACE activity.
Turmeric *(Curcuma longa L.)*	Nelson et al., [31]	Curcumin from turmeric was evidenced as a potential therapeutic development with a stable metabolism during consumption and promising low toxicity.
	Mishra et al., [7]	Curcumin reduced oxidative stress by indication of increased LPx, reduced GSH, and expression of antioxidant enzyme, SOD, catalase, and glutathione reductase through modulation of NRF2 pathway and KEAP1 regulator.
Galangal *(Alpinia galangal L.)*	Ivanovi [32]	Galangal contains prevails monoterpenes such as limenon, α-pinene, α-terpineol and 1,8-cineol.
	Singh et al., [33]	Ethanolic extract of galangal demonstrated cognition improvement in Alzheimer-induce mice, indicated by decreased levels of AChE, MOA enzymes, and increased activity of antioxidant enzymes, SOD, catalase, and vitamin C.
Sour plum *(Garcinia atroviridis)*	Tan et al., [34]	Sour plum demonstrated higher antioxidant capacity due to phenolic content such as (-)-β-caryophyllene, β-caryophyllene alcohol, and α-humulene with sesquiterpenoids as primary constituents.
	Chatatikun et al., [27]	Sour plum extract inhibits tyrosinase and melanin content for hyperpigmentation activity as a source of natural compounds and antioxidant capacity.
Chillies	Hamed et al., [35]	Capsaicin and dihydrocapsaicin constitute 90% of compounds in chilies and are responsible for pungency, sensation of hotness, and antioxidant activity.
	Joshi & Gangabhagirathi [8]	Capsaicin has competently attenuated radiation-induced biochemical alterations: LPx, PPx, and radiation-induced loss of antioxidant enzyme activity and the endogenous antioxidant GSH, in particular.

The relationship between antioxidants, inflammation, disease, and ROS among plant compounds has been a continuous topic for years. Recent studies have shown that the extracted garlic protein and its hydrolysates, GPH-P and GPH-T, provide protective effects as antioxidants on H_2O_2-induced oxidative damage [26]. Nevertheless, sour plum has presented its higher antioxidant capacity through interactions of phenolics and flavonoid compounds, inhibiting tyrosinase activity and melanin content for hyperpigmentation activity [27-29].

A subsequent in-vivo study by Singh et al., [33] provided further evidence on the role of galangal-induced neuro-degeneration through an antioxidant property. Researchers uncovered that treatment of galangal extract associates well with reduced AChE and MAO activity in Aβ peptide-induced neurotoxicity in Alzheimer's mice model. The treated galangal extract group showed antioxidant properties due to scavenged or attenuated free radical generation and neuroprotective side advantages. AChE is the enzyme responsible for acetylcholine hydrolysis of brain neurons [36], while MAO is a flavoprotein that catalyzes neurotransmitter oxidative deamination process [37]. Indeed, these results strongly support the treatment of galangal extract in connection with AChE and MAO with oxidative stress.

Further work by Mishra et al. [7] elucidated the antioxidant mechanism by which curcumin may alleviate oxidative stress through NRF2, a master regulator of antioxidant response. Their investigations were focused on the oxidative stress in rat hearts under different thyroid conditions, which identified that increasing levels of LPx is a significant occurrence and reported it to be more vulnerable to ROS attack [38,39]. It is assumed that the antioxidant molecules of curcumin effectively reduced the level of LPx by turning off ROS in the hyperthyroid state and reducing hyperlipidemia in the hypothyroid state. Also, curcumin bioactive compounds demonstrated an increment of cellular GSH (antioxidant) levels by improving the transcription of glutamate-cysteine ligase, an enzyme in GSH synthesis [40].

The antioxidant mechanism from chilies' bioactive compound, capsaicin, has also been documented to involve the mitochondrial marker enzyme succinate dehydrogenase and scavenging free radicals [8]. The researchers observed that capsaicin shows significant inhibition formation of peroxidation products from LPx, formation of protein carbonyl products from PPx, and scavenging lipid peroxyl radical [41-43]. Nevertheless, the study demonstrated that the formation of capsaicin phenoxyl radical plays a crucial role for both capsaicin and its phenoxyl radical in-vitro, principally by scavenging oxidizing free radicals. Based on the evidence outlined above, the singgang dish is an attractive and potential target for antioxidant therapy in one meal.

3. Singgang and anticancer

As one of the nutritious meals, Jamain et al., [44] investigated fish singgang extracts as a potential antiproliferative against colon cancer cell lines (HT-29, HCT-116, CT-26) using a colorimetric micro-titration method and morphological observation. Results supporting the singgang dish with chub mackerel fish gives the best anti-proliferation effect compared to the singgang dish with Indian mackerel fish. The results were supported by Hall et al., [45] and Huerta-Yépez et al., [46] who reported that consumption of fish can reduce the risk of getting colorectal cancer because fish has n-3 long chain fatty acids and is rich in omega-3 and omega-6 contents. Eventually, it could induce cell death in tumor cells via the apoptotic pathway and interfere with the cell cycle components that can modify the growth of tumor cells [46]. Thus, results from the studies have provided insights into preliminary data on the role of the singgang dish as a potential anticancer dish.

Further, evidence from previous studies supports the role of each spice and herb ingredient in the singgang dish in regulating cell apoptosis, proliferation, and angiogenesis in several cell types, as depicted in Table 2. Therefore, the data observed shows that the singgang dish's anticancer might depend on the synergy effects of anticancers and antioxidants between the herbs, spices, and fish used. Szychowski et al., [9] observed that garlic extract induced Apoptosis by increasing intracellular ROS through the mitochondrial-dependent intrinsic apoptotic pathway, which leads to caspase-3 stimulation in SCC-15 cells. Furthermore, the defensive effect of garlic extract was along with the NRF2-ARE pathway and the increasing of mRNAs in heme oxygenase-1 and NAD(P)H quinone oxidoreductase 1; enzymes crucial in the cellular antioxidant system [9].

Further studies by Norouzi et al., [47] present curcumin as an essential miRNA modulator in breast cancer. This investigation indicates that curcumin can relate to some oncogenic and tumor-suppressive miRNAs involved in changed stages of breast cancer. Then, the up-regulation of miR181b [48], miR-34a [49], miR-16, miR-15a [50], and miR-146b-5p, and the down-regulation of miR-19a and miR-19b [51] have been influential in the treatment of several breast cancer cell lines with curcumin. Therefore, this investigation confirmed that curcumin in turmeric could stimulate the attenuation of metastasis and tumorigenesis and initiation of Apoptosis in breast cancer.

Apart from reports on colorectal cancer and breast cancer, bladder cancer has also been recently shown to be treated by spices and herbs that are used in singgang dishes, chilies, and garlic extract. The researchers observed that PKA signaling is the important pathway involved in garlic, especially in T24 cancer prevention, which significantly up-regulated AKAP12 (tumor suppressor) and down-regulated RAB13 (tumor enhancer) as essential cancer markers [52]. In the context of cancer, AKAPI2 could induce cell cycle arrest and Apoptosis in cancer cells [53,54], while RAB13 plays a central role in promoting the tumorigenicity of cancer cells [55]. These results reveal that the consumption of garlic extract has a high degree of preventing the in-vivo development of cancer and has a safety profile, too.

Subsequent studies on TSGH8301 and T24 bladder cancer cells have also focused on the role of active compounds from capsaicin chili pepper. Previously, numerous signaling pathways were identified to be involved in capsaicin-mediated cellular responses, including oxidative stress, ROS generation, and mitochondrial damage [56-58]. Lin et al., [59] demonstrated that tNOX catalyzes the oxidation of NADH, reduces NAD^+ generation, and attenuates NAD^+ -dependent SIRT1 deacetylase activity. These cellular functions eventually brought capsaicin-induced enrichment in multiple cancer phenotypes, including Apoptosis and suppression of cell proliferation, migration, and Apoptosis.

The potential Apoptosis of cancer cells has also been documented to be involved in ovarian cancer cells (A2780/CP70 and OVCAR-3) by galangin, a flavonoid from galangal.

Table 2. Studies on herbs and spices of singgang dish ingredients as an anticancer activity.

Herbs	Authors (year)	Cancer types	Possible role and mechanism proposed
Garlic *(Allium sativum L., Alliaceae)*	Kim et al., [52]	T24 bladder cancer	Garlic extract involving cancer prevention is through PKA signaling pathway with AKAP12 and RAB13 gene regulation using tissue microarray and gene network analysis.
	Szychowski et al., [9]	SCC-15 squamous carcinoma	Garlic extracts induced Apoptosis by increasing intracellular ROS through the mitochondrial-dependent intrinsic apoptotic pathway, which leads to caspase-3 stimulation.
Turmeric *(Curcuma longa L.)*	Norouzi et al., [47]	Breast cancer	Curcumin could relate the expression of some oncogenic and tumor-suppressive miRNAs and attenuated the metastasis and tumorigenesis in several breast cancer cells.
	J. Y. Wang et al., [16]	Non-small-cell lung cancer A549	Curcumin treatment indicates that oxidative stress is involved in the curcumin-induced Apoptosis of cells by increasing intracellular ROS levels, SOD and γ-GCS activity and inhibition expression of γ-catenin, p-GSK3γ (Ser9) protein, cyclin D1 and c-Myc via Wnt/γ-catenin pathway.
Galangal *(Alpinia galangal L.)*	Huang et al., [10]	A2780/CP70 and OVCAR-3 ovarian cancer	Galangal treatment mainly induces Apoptosis via the p53-dependent intrinsic apoptotic and Akt/p70S6K pathways, in which p53 is a key regulatory protein.
	Ahlina et al., [15]	4TI metastatic breast cancer	Galangal exerts potential anti-metastasis activity by suppressing MMP-9 expression and inhibiting the migration of metastatic cancer.
Sour plum *(Garcinia atroviridis)*	Parasramka et al., [61]	PaCa	The synergism of garcinol-gemcitabine attenuates proliferation and induces Apoptosis by regulating key markers involving PARP, VEGF, MMPs, ILs, caspases, and NF-B.
	Tsai et al., [62]	Colorectal cancer	Garcinol treatment induced inflammation-related colon tumorigenesis in rats through COX-2, cyclin D1, and VEGF down-regulated expression via the Wnt/β-catenin pathway.
Chillies	Lin et al., [59]	TSGH8301, T24 bladder cancer	Capsaicin augments spontaneous Apoptosis through tNOX, and SIRT1 down-regulates expression and extends the progression of the cell cycle.
	Y. Wang et al., [17]	Osteosarcoma cells	Co-treatment of capsaicin and cisplatin triggered pro-survival autophagy over ROS/JNK and p-AKT/mTOR signaling in osteosarcoma cells and inhibited tumor growth in an osteosarcoma xenograft model.

4. Conclusions

Singgang is a potential health dish made by boiling selected fish, herbs, and spices ingredients and is suitable for health. This review has provided compelling recent evidence for the emerging roles of the singgang dish, focusing on the antioxidant and anticancer hallmarks of herbs and spices used in the dish. As mentioned above, the ingredients used in the singgang dish have been shown to contain high antioxidants based on the recovery mechanism of free radicals in the body. However, various pathways involve the anticancer properties of the selected herbs and spices in the context of Apoptosis and metastasis. Tables 1 and 2 summarize recent studies examining certain herbs and spices and their role in antioxidant and anticancer types. Given the critical roles, it is highly probable that the singgang dish will emerge as a potential dish with therapeutic benefits. For future studies, it is recommended that screening bioactive compounds present in sing gang dish extracts using chromatography would give more insight into specific compounds' actions towards health properties.

Acknowledgments

This study was supported by grant number UniSZA/RMIC/2018/04 from the Centre for Research, Excellence, and Incubation Management (CREIM) at Universiti Sultan Zainal Abidin. A special thanks go to the Dean of the Faculty of Medicine and Deputy Dean of Research and Innovation for the assistance provided in this study. The acknowledgment also goes to all staff from Teaching Laboratory 1, Faculty of Medicine and Faculty of Health Sciences, UniSZA.

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Abbreviations

AKAPI2	A kinase anchor protein 12
ACE	acetaminophen
AChE	acetylcholinesterase
Akt	serine-threonine kinase B
Aβ	amyloid β
ARE	antioxidant response element
Bcl-2/Bax	B-cell lymphoma 2/Bcl-2-associated X protein
COX-2	cyclooxygenase 2
Cyclin D1	D-type cyclins protein
c-Myc	cellular myelocytomatosis
GPH-T	garlic protein (trypsin)
GPH-P	garlic protein (pepsin)
GSH	glutathione
H_2O_2	hydrogen peroxide
ILs	interleukins
KEAP1	Kelch ECH associating protein
LPx	lipid peroxidation
miR181, miR-34a, miR-16, miR-15a, miR-146b-5p, miR-19a, miR-19b	types of micro ribonucleic acids in cancer cell
miRNA	micro ribonucleic acid
MMP-9	matrix metallopeptidase 9
MAO	monoamine oxidase
mRNAs	messenger ribonucleic acid
mTOR	mechanistic target of rapamycin
NAD(P)H	nicotinamide adenine dinucleotide phosphate
NAD^+	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide + hydrogen
NF-B	nuclear factor kappa light chain enhancer of activated B cells
NRF2	nuclear factor erythroid 2-related factor 2
p53	53-kDa ribosomal protein
p70	70-kDa ribosomal protein
p70S6K	70-kDa ribosomal protein S6 kinase
p-GSK3β (Ser9)	phospho- glycogen synthase kinase 3 beta (Ser9) protein
p-GSK3γ (Ser9)	phospho- glycogen synthase kinase 3 gamma (Ser9) protein
PaCa	pancreas cancer

PARP	poly-ADP ribose polymerase
PKA	protein kinase A
PPx	protein peroxidation
RAB13	ras-related in brain
RNS	reactive nitrogen species
ROS	reactive oxygen species
ROS/JNK	reactive oxygen species/c-Jun N-terminal kinase
SIRT1	sirtuin 1
SOD	superoxide dismutase
tNOX	tumor associated NADH oxidase
VEGF	vascular endothelial growth factor
Wnt/β-catenin	wingless and Int-1/ beta-catenin
β-catenin	beta-catenin
γ-catenin	gamma-catenin
γ-GCS	gamma-glutamylcysteine synthetase