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A Comparative Study of The Pharmacotherapeutic Effects of Capsicum and *Zanthoxylum spp*: A Systematic Review from Usage as Spice to Potential Clinical Use in Drug Development

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Abstract: ***For centuries Chili and Sichuan peppers have been used in cooking largely in Asia due to their attractive pungent orosensations. It is a reported fact that Chili pepper and zanthoxylum bungeanum produces a combined typical complex taste (called as 'Ma La') in traditional Sichuan cuisine. In addition to their unique hot sensory properties, many reports suggests accumulating evidences of medicinal and pharmacological significance attached to these two pungent spices. In this review we comprehensively compare the chemical compositions, organoleptic properties, pharmacological and clinical applications of Sichuan pepper and Chili pepper.***

Keywords: Hydroxyl-α-sanshool, capsaicin, spices, polyphenols, flavonoids, clinical use

1. Introduction

Capsicum and Zanthoxylum popularly referred to as Chili pepper and hujiao or Sichuan pepper are two popular spices feature and are well admitted for their distinctive singular flavor and likable esthetic feel in the mouth. They both go way back, for centuries have been used for color and flavor purposes and by other for preservation purposes, however the most significant use is its application for healing purposes. The genus Capsicum is composed of over 30 species, which was first discovered in Guatemala and New Mexico during the 7500 B. C. Domestication of peppers is followed back to as far as eight thousand years ago (Liu, Kang & Kang., 2013). For decades, there are five tamed yields, specifically *Capsicum annuum* which is the most popular chili spice to grow, capsicum chinense are also cultivated for aroma purposes but possess no burning sensation as *Capsicum annuum*, *Capsicum frutescens* with Scoville ratings of between 30, 000 and 60, 000 units, *Capsicum baccatum* is a perennial plant listed as a 'weed' among the Global Compendium of Weeds and the *Capsicum pubescens*, this yield is the least cultivated and least widespread of all the five cultivated Capsicum varieties, which covers a wide array of natural shape and size and then shading and taste. At present the largest producers of chili pepper are Mexico, China and India. Sichuan pepper popularly known as Huajioa is a member of the Rutaceae family specifically the zanthoxylum species. This species is broadly grouped into two the red Huajioa and green Huajioa that *Zanthxylum bungeanum* and *Zanthxylum schinifolium*, which are for the most part circulated in the Southwest regions of China. *Zanthoxylum armatum* is privately called Timur in Nepal (Nirmala Phuyal,) and *Zanthoxylum piperitum* commonly referred to as Sanshō among the Japanese people (Friedman et al.2019). Sichuan pepper has since been used typically for seasoning purposes in Sichuan dishes for thousands of years now.

Respectively, even though both Chili and Sichuan peppers are referred to as pungent spices, their exerted sensations are clearly extraordinary. Sharpness of Chili peppers are described as 'warmth' or 'chomp' sensations delivered by accumulated alkylamides. The pungency of chili pepper largely depends on the capsaicin component present, The pungency is believed to be the defense mechanism of chili peppers against animals, microbes and fungi (Friedman et al., 2019) Comparatively, the *Zanthoxylum spp* causes a numbing sensation of the buccal cavity and activation of some specific type of neurons, which are distinctive from those excited by Chili pepper (Koo et al., 2007) The sensation produced by Zanthoxylum pepper is originated primarily from some specific types of unsaturated alkylamides, referred to commonly as sanshools. The distinct aroma of these alkayamides arise from the many volatile compounds making up the chili pepper and Zanthoxylum pepper or Sichuan pepper.

At present, a number of population-based cohort studies suggested that the dietary consumption of spicy foods was inversely associated with mortality and hypertension. Accordingly (Lv et al., 2015), besides the use of both peppers for purposes of flavor and color, they have been used for many other significant activities. For example, chili peppers are used traditionally as appetizers and medicinally in aiding blood circulation in the body. The volatile compound Capsaicin is said to be very significant in the pharmacological industry for drug development of pain reliefs and anti-inflammatory (Luo, Peng & Li., 2011). While Sichuan peppers are known for their culinary benefits among Asians and Native Americans. Zanthoxylum have been adopted in the productions of well over 30 prescriptions for management of diarrhea, ascariasis, itching, and trauma by Chinese people (Deng et al., 2019). The bioactive compounds in Zanthoxylum include as alkylamides, which have shown to have potentials in the management and pre-clinical treatment and prevention of cancers.

This review therefore seeks to make up for this void of knowledge, comparing the difference and similarities, especially with regards to their use in cuisines, dishes, and pharmacological potencies and activities as well as further discuss the possible synergistic combined effects of both spices pharmacological implications.

2. Compounds, bioactivity and chemical makeup

2.1 Alkaloids

Generally, the fruits of Capsicum and Zanthoxylum are heavily rich in carotenoids and phenolic compounds which are responsible for the coloring of the dishes and alkaloids which provides them with the distinctive characteristic pungency and properties.

2.1.1 NAAs

NAAs compounds in both peppers are viewed as very significant compounds which are very promising. The NAAs are mainly described by their amide or peptide bonds ((–CO–NH–) /–C (=O) NH–) that are planar and relatively stable.

The major difference between the structures of Zanthoxylum and Capsicum is in the head region. While possessing similar neck regions. Zanthoxylum however is mainly characterized by three sections of double bonds at the fatty acids chain ends, the molecular structures of the two alkylamides are presented in table 1.

Which is mainly concluded from the effect of chemical groups on the pungency (Chen et al., 2019a, Chen et al., 2019b). It is proven that having a cis-double in the sanshool chains definitely are an important feature rather than a requirement which excites its unique sensory power. It is worth mentioning that besides the fact that the alkylamides are responsible for pungent sensation, there are some alkylamides with little to completely no pungency such as capsiate and other analogues of capsaicin and other relevant alkaloids

In chili pepper, alkaloids make up about 90% of the alkylamides composition of camsicum. The other alkaloids are vanillin caproate, vanillin nonanoate, vanillin decanoate, p-methylcapsaicin group, p-methylcapsaicinene chain group, p-methylcapsaicinene saturated chain hydrocarbon group, p-toluene.

Significantly, besides the alkylamides, quinolines, isoquinoline, benzophen and anthridine are the other alkaloids present in the Zanthoxylum genus which are largely responsible for the pharmacological potencies of the species (Diaz, Miranda &Diaz., 2015, Qing et al., 2017). These alkyl amides are mostly found in the whole plant, the roots, and leaves and stem all inclusive.

2.3| Polyphenolic composition

The polyphenols of Capsicum and Zanthoxylum are different in contents and compositions. The polyphenolic compounds of chili peppers are largely affected by their genetic makeup, their aging cycle and extent of coloring (Aza-Gonzalez, Nunez-Palenius &Ochoa-alejo., 2012). Generally capsicum species are seen as decent sources of natural phenolic compounds, such as flavonoids which is among the commonest polyphenolic substances. Some critical flavonoids in chili pepper are at first recognized as flavonol and flavanone glycosides and flavanols. Additionally, some polyphenolic acids have also been recognized. From **Table 2 (**a, b, c**)** the various polyphenols and sub-groups can be seen for both peppers.

Besides the above flavonoids and phenolic acid in Capsicum species, chili pepper is suggested to have the potential to digest and accumulate anthocyanins such as delphinidin-3-transcoumaroylrutinoside-5-glucoside and delphinidin-3-cis coumaroylrutinoside-5-glucoside (Aza-Gonzalez, Nunez-Palenius &Ochoa-alejo., 2012)

Quercetin is the dominating flavonoid, the presence of quercetin is the luteolin which occurs in the form of three compounds namely: luteolin-7-O-dihexoside, luteolin-6-C-hexoside-8-C-pentoside, and luteolin-7-O-malonyl-dihexosyl-pentoside (Lakhanpal & Rai., 2007).

There has been a number of research conducted on the quantification of polyphenols in Zanthoxylum bungeanum, nonetheless very little work have been found on polyphenol compositions.

Recently, Chi-Tang et al (Ji & Ho., 2019) identified the phenolic composition in pericarp of *Zss bungeanum* using UPLC-MS method.

2.4 | Carotenoids (essential pigmentation)

In addition to pungent sensation, another significant index of the commercial quality of peppers are their characteristic color. Color is a common visualized evaluation indicator which largely impacts the purchasing behavior of consumers.

During ripening the fruit of chili pepper undergoes transformations in their metabolic processes, structural and physiological changes influencing pigment composition during the ripening processes. (Zhang et al.2017, Hong et al, 2017). Both Chili pepper and Sichuan pepper start off green, as they ripen chili pepper turns red, orange or purple and Sichuan pepper turn brownish red.

Among the different carotenoids, the red pigmentation of *Capsicum spp* is from the lipophilic capsanthin and accumulated during its synthesis. During this ripening stage the capsanthin forms about half of the complete carotenoid content.

2.5 | Aromatic compounds

Capsicum and Zanthoxylum species are both heavily used in preparing cuisines due to their additional taste and coloring properties when used in cooking, these two peppers also have very distinct attractive smell or aroma when fried in hot temperatures. Another essential purpose for the use of these peppers, is the use of it to minimize the strong fishy smells thereby reducing the incidence of nausea after consumption of cuisines.

The aroma from Chili and Sichuan peppers are from their volatile components, the components responsible for aroma in both peppers are well looked into. For this review, various compounds were identified and the chemical groups they belonged to: the compounds containing nitrogen, acid components, alcohols, lipoxygenase cleavage products, esters, furans, terpenes and some hydrocarbons. Just like the Sichuan pepper have also been reported to be composed over eighty types of volatile compounds too. (Gogus, 2015)

Regarding the Sichuan pepper, around 120 aromatic compounds are identified in early reports. Work on aromatic composition has demonstrated that extracts from Sichuan peppers are highly composed of terpenes, with a linalool component of around 75%. In the report by Yang et al. (2008), a total of 120 aroma compounds has been found in the essential oils from different species of Sichuan Pepper (Yang,.2008).

The aroma of these two pepper spices gets even pronounced with hot temperatures and by extension in cooking. Li et al. (2018) recently carried out a study which was designed to evaluate in aromatic compounds of Sichuan pepper during different temperatures in cooking.

Their study reported myrcene, limonene, 1, 8-cineole, linolool, 2-phenylethanol, trans-carveol and 4-methylacetophenone are the active aroma components of the Sichuan pepper. In this same report, it was also stated that 1, 8-cineole and linolool are the most intensive components whereas 2-phenylethanol and 4-methylacetophenone are the key aroma-active components in the Sichuan pepper (Li et al., 2019). These are obtained while taking into consideration that the cooking temperature is as important as the compound itself when using it in the preparation of Chinese cuisines.

3. Pharmacotherapeutic applications and developments

3.1 | Sensory physiology and role in Analgesic effects

3.1.1 Mechanism on organoleptic effects

The transient receptor potential (TRP) cation channels are categorized into six subgroups with twenty-eight members in mammals: TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and TRPA (ankyrin). The TRPV subgroup is the most characterized subgroup of TRP channels, constituting of six homologous members (TRPV1-6). TRPV channels are generally nonselective cation channels which are largely expressed in both sensory and non-sensory cells and they play a role in nociceptive responses to chemical and physical stimuli such as heat, cold, irritant chemicals, and osmotic pressure. (Caterina & Pang., 2016, O'neil & Heller., 2005).

In human physiology the TRPV1 is said to be involved in transmission and modulation of the physical processes underlying the sensation of pain. It is also involved in the integration of diverse painful stimuli. (Cui et al., 2006) The TRPV1 found in the nociceptive neurons of the peripheral nervous system have been found on some tissues, including the central nervous system (CNS) in humans. In addition, TRPA1 is a member of transient receptor potential channel group which constitutes 14 N-terminal ankyrin repeats and is reported to function as a mechanical and chemical stress sensor (García-Añoveros J, Nagata K 2007).

For the past decades, the physiological activities of Capsicum and Zanthoxylum species and their abilities to stimulate pungent sensations have been broadly explored. It is known capsaicinoids happen as hot sensations, particularly for capsaicin activates the TRP family proteins with particular reference to TRPV and TRPA1 receptors. (Yang & Zheng., 2017) It ought to be profoundly noticed that capsaicin has an extremely high partiality, affectability, and selectivity for TRPV1, though it cannot trigger the homologous TRPV2–TRPV6 receptor (Yang & Zheng., 2017, Liapi & Wood., 2005).

How the capsaicin is able to activate the ion channel and this has been fascinating to many scientific researchers. There have been a few scientific exploratory methods utilized in this field including mutagenesis, cryo-electron microscopy, computational docking, patch clamp recording, and sub-atomic powerful reproduction (Yang & Zheng., 2017). Through these progressions, a steady knowledge have been made in evaluating how capsaicin attaches itself to the TRPV1. Initially, by utilizing cryo-electron microscopy, the distinction of TRPV1 channels in bound and unbound with capsaicin states are shown. (Yang & Zheng., 2017). Capsaicin presents a 'tail-up-head-down' setup when it attaches with TRPV1. There are three unique types of interactions between substitutional groups in capsaicin and TRPV1. One example include the pull-and-contact interaction between the 'head' which is the vanillyl group of capsaicin and the S4-S5 linker of the capsaicin. Secondly, the bonds are formed by the binding of the 'neck' (amide part) and S4 part of TRPV1. Thirdly the van der Waals binding interaction of tail of capsaicin (fatty chain). Researches have been able to demonstrate that capsiacin exerts conformational rearrangements that runs from the S4–S5 linker towards the S6 bundle, and eventually reaching areas of the selectivity filter. (Yang et al., 2019, Kasimova et al., 2018).

3.1.2 | Analgesic effects

Preclinical and human-derived evidence supports TRP channels as targets of analgesics. TRPV1 activation has been to be significantly involved in signals of acute pains and inflammations resulting from extreme pains. An essential role of TRPV1 in pain sensation has been further proven by either deletion of the TRPV1 gene (knock-out mice) or "knock-down" of TRPV1 by RNA interference. (Christoph et al.2006)

The pain management of capsaicin has been mostly studied. Numerous studies in Vitro and in vivo have demonstrated the analgesic effect of capsaicin at high doses application (e. g. a commercial available patch with 8% capsaicin.

Capsaicin acts as an agonist of TRPV1, by firstly inducing TRPV1 channels in the sensory neurons subsequently producing a lasting desensitization (Premkumar & Sikand., 2008, Sanz-salvador et al, 2012, Tian et al., 2019). Compared with capsaicin, only limited literature regarding the analgesic action and the corresponding mechanisms of the alkylamides in the Zanthoxylum species have been presented by various studies even though Sichuan pepper has been used in tooth aches inflammatory pains and rheumatoid arthritis for centuries. Tsunozaki et al demonstrated in their study of α-SOH interaction with sodium sensory neuron channels to prevent all acute and inflammatory pains in mice models (Tsunozaki et al., 2013). Also, Tong et al mentioned that bergapten in *Z. schinifolium* is able to inhibit the body sprain as a result of acetic acid in mouse model (Zhang et al., 2017). A recent study by L Hong et al investigated the analgesic effects of the volatile oils contained in *Zanthoxylum bungeanum*. (Hong et al., 2017).

3.2 | Lipid catabolism and Anti-obesity effects

In metabolic syndrome, Obesity and hyperlipidemia are mainly the components responsible for the increased risk of progression of conditions such as CVDs and type 2 diabetes, and non-alcoholic fatty liver disease. Metabolic adipose tissue and liver contains TRPV1 and TRPA1 (Dhakal & Lee., 2019), making them a site of interest for potential metabolic interventions. Since the triggering or activation of both channels is reported to cause an anti-obesity response or generally reduce the incidence of obesity. However, currently there are several works conducted on the role of capsaicin and its potential ability to manage energy and body. For example, a number of human intervention trials suggest daily consumption of capsaicinoids may increase energy expenditure by around 30 per cent for an hour (Yoshioka et al., 1995) and lipid oxidation by around 20% (Lejeune, Kovacs, & Westerterp-Plantenga, 2003. Derbyshire, Tiwari (2014) report suggested that daily dietary intake of capsaicin may be significant in weight management through the lowering of energy intake. In another report, intake of 4 mg of capsaicin daily significantly improved HDL levels and reduced triglyceride and C-reactive protein levels in healthy human (Yang et al., 2017). Nonetheless, after other works and trials of the effects or influence of capsaicin on energy uptake, it demonstrated to be fruitless. The study of Rigamonti et al demonstrated that 2 mg intake of capsaicin by obese teenagers and young adults could not yield any substantial effect on energy intake or appetite (Rigamonti et al., 2018).

On the other hand, unlike capsaicin, there is little information or research on the ability or potential of Zanthoxylum alkylamides in anti-obesity or energy intake. Some research works however reported the ability of Zanthoxylum extracts in the lowering of lipids in cellular models (3T3-L1 adipocytes and HepG2 cells) (Kwon) and mouse models (hyperlipidemic rats) (Wu et al.2015)

SM Meenaksh (2015) combined the extracts of Capsicum and Zanthoxylum for his study and reported that it had the ability of lipid-lowering effect (Meenakshi., 2015). Importantly, the experiment was conducted in different ratios of 8: 1, 7: 2, and 6: 3. Recently, Wang et al., (2019) reported that (α-SOH) plays the key role in the anti-obesity regulation of lipid metabolism in Sichuan pepper. (Wang et. al.2019)

However, till now, there is no the clinical trial to verify the role of Sichuan pepper extracts and its ability to regulate lipid metabolism to cause weight loss. The effects of such compounds on humans is yet to put describe in the literature.

3.3 | Roles in diabetes prevention

WHO defines diabetes Mellitus as an acute or chronic disease which manifest when the pancreas produces little insulin or cannot use the insulin produced by the body (WHO, 2016).

Statistics indicates that over 400 million people, specifically adults suffer from diabetes mellitus and claims about 1.5 million lives yearly. (WHO., 2016.2017). However hope lies in not just the fact that several research works have proven the essential role of TRP ion channel in the progress and development of both type 2 and 1 diabetes but the potentials of capsaicin and sanshools in targeting the TRPA1 and TRPV1. A study conducted on animals provided promising potentials in glucose metabolism in several animal models used. Another study presented the potentials of dietary capsaicin in reducing obesity induced by insulin resistance in high-fat fed obese mice.

(Kang et al., 2010). Song et al reported from their study that both high-capsaicin (0.02%) and low-(0.01%) diets essentially prevented or slowed down the increasing of fasting blood glucose and the levels of insulin in obese diabetic ob/ob mice (Song et, al., 2017). Another research work reported that 1% in daily diet of red peppers prevents hepatic insulin resistance in Sprague Dawley rats with Alzheimer's and diabetes diseases (Yang et. al., 2015). A more recent research work provided evidence that capsaicin is more potent than capsiate in regulating insulin levels in rats suffering from type 1 diabetes (Zhang et al., 2017). Interestingly just like capsicum, several other literatures reported the anti-hypoglycemic potentials of *Zanthoxylum bungeanum*. For instance, Ren et al. in his research found that the alkylmides of Zanthoxylum caused a decrease of fasting blood glucose levels in orally fed diabetic mice and a reduced organs imposed by diabetes. (Wu et al., 2015, Ren, Zhu & kan., 2017). However other works also found that the alkylamides in Zanthoxylum had the potential to facilitate protein synthesis in rats both healthy and diabetic using the PI3K/PKB/mTOR pathway.

Some clinical studies also reported that chili pepper had the potentials to manage the effects from postprandial hyperinsulinemia. (Sanati, Razavi & Hosseinzadeh., 2015). In addition, using capsaicin medications increases the absorption of glucose and on the other hand increasing glucagon release in glucose loading tests, using healthy humans (Panchal, Bliss & Brown., 2018, Domotor, Szolcsanyi & Mozsik., 2006). Other scientific reports indicates that capsaicin can induce a reduction in gestational age neonatal morbidity rate (Zhang et al., 2017, Yuan et al., 2016. However, there exist no clinical research work done on prevention and management of diabetes using Sichuan pepper only.

3.4 | Cardiovascular diseases

For several decades now, CVDs (cardiovascular diseases) have consistently been the major causes of mortality and morbidity (Liu, Kang & Kang., 2013, Ng & Riuter., 2015). diabetes, obesity, dyslipidemia, atherosclerosis are all common pathogenesis of different kind of CVDs. Atherosclerosis is an inflammatory vascular disease which is basically characterized by lipid accumulation, leukocyte activation, endothelial dysfunction and the ability to produce inflammatory mediators and reactive oxygen species.

Previous studies reported that capsaicin has the ability to activate Ca^{2+}/PI3K/Akt/eNOS/NO signals so as to inhibit the progression of inflammatory cytokines and adhesion molecules in the endothelial cells (Zhang et. al., 2019, Wang et al., 2017).

There are several advances in the mechanisms employed by capsaicin to regulate and activate the TRPV1 which plays an essential part in managing the storage of lipid and by extension, limiting the incidence of atherosclerosis lesions.

Similarly Ma et al. (2011), reported that capsaicin ability to activate the TRPV1 for a long-term greatly causes a reduction in lipid storage and atherosclerotic lesions in mice with $ApoE^{-/-}$(Ma et al., 2011). Other capsicum alkylamides such as capsaicin and dihydrocapsaicin were reported to have the potential to inhibit plaque formation using the PPAR/LXRa pathway in $ApoE^{-/-}$mice fed (Domotor, Szolcsanyi & Mozsik., 2006). On the other hand, in an in vitro study, Zanthoxylum alkylmides such as *Z schinifolium* showed potentials in the inhibition of activities of platelets aggression, with other reports indicating *Z schinifolium* displayed potentials in minimizing inflammation and proliferation of the vascular cells and an inhibitory effect on thrombosis and hyperlipidemia when the oil extracts of *Z schinifolium* was combined with the leaf extracts of *Gink goliloba* in mice fed with high fat (Zhang et al., 2017).

3.5 | Gastrointestinal effects

The TRPV1 channels are largely present in the GIT, primarily in the aerent neurons and in the ENS neurons, and fairly present in the epithelial and endocrine cells too. Several research works have proven that both the TRPA1 and the TRPV1 play an active role in nociception, pain, mechanics in sensation taste and pain. However evidences suggest potential of both Capsicum and Zanthoxylum alkylamaides to influence and modulate the mechanisms and processes of TRPA1 and the TRPV1. (Ma et al.2011, Julius.2013). Chili pepper showed potentials of protective effects on the mucosa of the gastric and very essential pro-inflammatory cytokines down regulation in gastric mucosa of rats.

(Mendivil et al.2019). Diets with high capsaicin has the ability to change the diversity of microbiota of the gut by regulating the homeostatic balance of glucose in obese mice with diabetes. The six week administering of chili to sixteen patients with diarrhea-predominant irritable bowel syndrome caused a reduction of the postprandial abdominal burning and increased sensory threshold of the rectum (Aniwan & Gonlachanvit., 2014).

The extracts of *Zanthoxylum bungeanum* containing both water and oils are reported to have the potential to effectively act against sulfate sodium-induced ulcerative colitis mice (Zhang et al.2017, Lu & Chao., 2020).

Unfortunately, the basic protective potentials or abilities of the individual composition of Sichuan pepper is still very vague. However, besides the potential of *Zanthoxylum bungeanum* in the management of ulcers and other gastrointestinal diseases, its consumption or sage in meals can significantly increase gut and colonic motility and activities. There are several reports of the significant potential of β-SOH (hydroxyl-β-sanshool) in colonic contraction. However, the mechanisms and abilities of these alkylamides may be structure dependent. The β –SOH has the potential to only inhibit the KCNK3 channel while α-SOH (hydroxyl-α-sanshool) blocks two other channels, KCNK9 and KCNK18, which may be the reason for the difference in colonic contraction behaviors.

3.6 | Remedies for Cancer Therapy

Cancer is the second leading cause of death in the United States surpassed only by cardiovascular diseases. The transient receptor potential (TRP) mechanisms interferes with many processes of cancer development including extreme cell proliferation, change in tumor positions and invasions, the formation of new blood, survival of the cell and the potential to aid in inhibition of cell death. Many research works have proven that chili pepper, mainly the capsaicin alkylamides components shows abilities to inhibit tumor formation activities in cancer cell lines. Though some few other research suggests that high consumption of capsaicin has the ability to promote breast, skin and colon cancers.

Capsaicin alkyl amide of capsicum has displayed potentials of ability to cause cell death of many cancers such as, cancer of the liver (Lee et al., 2004), esophageal cancer (Wu et al., 2006), cancer of the bladder (Lee et. al., 2004), colonic cancer (Hwang et al., 2007), lung cancer (Athanasiou et al., 2007), skin cancer (Hail & Lotan., 2002), leukemia (Ito et al., 2004) cells and leaving the normal or healthy cells untouched (Clark & Lee., 2016).

Similar works has been conducted to investigate the potential of the alkyl amides of *Zanthoxylum bungeanum* on tumors. A research reported that some oil and water extracts of Sichuan pepper showed an anti-tumor potential on the cells of PC-3, Hela, MFC-7, and HEp-2. . Other reports also showed that the sanshool extracts of *Z. bungeanum* also displayed anti-tumor potentials against SW620 and HepG2 cells. The volatile compounds such as terinen-4-ol and D-limonene of Sichuan pepper extract components also displayed mitigating effects on the proliferation of the cells of HaCaT.

Despite the several proves of the abilities of these two peppers by several research works in the management and treatment of cancers by many researchers, unfortunately there is no application of it clinically due to the present issue of sides effects such as irritation of the gastro intestine and causing stomach cramps accompanied with burning sensations.

(Miller & Snyder., 2012). This worrying setback however may be circumvented by researching into other analogs of capsaicin that are without burning sensation effects but still retain those anti-carcinogenic abilities.

4. Conclusion and future research directions

Chili and Sichuan peppers have gained the attention of many scientists in food and pharmacological industries due to their unique flavor, sensational characteristics as well as their vast pharmacological activities and potential in drug development for medicinal and clinical use. In summary, in this review we present that the main chemical classifications of both peppers are carotenoids, alkaloids and phenols, nonetheless the composition of each class are not necessarily same. The mechanisms of each spice to induce the pungent sensation however is different. There are clear and adequate evidences that chili pepper achieves its sensation by activating the TRPA1 and TRPV1 ion channels whereas that of the Sichuan pepper is still unclear with several controversies.

Currently, there are many essential progresses made the field of the study of the medicinal abilities of both peppers targeted at possibilities of extracting only medicinal compositions of both peppers and possibly modify for drug developments of medications used in the treatment and management of pain, dyslipidemia, obesity, diabetes, CVDs, GIT function, cancers and many other ailments. However the key components responsible for the medicinal potentials of chili pepper exacts irritation of the GIT and eliminations of this effect however should be most considered as the first step in the practical application of it in drug development for clinical use. In addition, in some parts of the world (mainly China) both spices are used at the same time in Sichuan cuisines. Thus, the interactive possibility and effects are worth researching into. In comparative terms, there is little information on the alkyamides found in *Zanthoxylum bungeanum* due to the less research work done. More investigations on the alkyamides present in Sichuan pepper may provide the mechanism of function of the Sichuan pepper and its possible pharmacological applications.

Conflict of competing interest

The authors declare that they have no conflict of interest.

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Author contributions

MZ and JW designed the study. MZ and NI contributed in literature searching, relevant information selection, and independent reviewing. SA and SH drew the chemical structures and MZ wrote a first draft of the manuscript. MZ and JW prepared the final draft. All authors have gone through the final manuscript and approved it.

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Tables

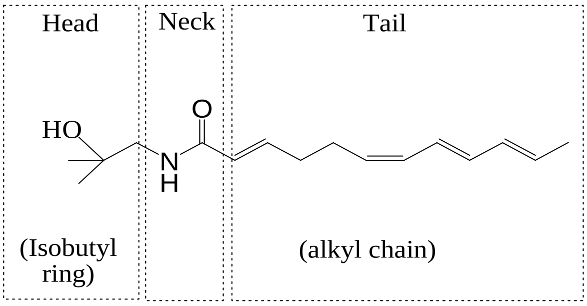
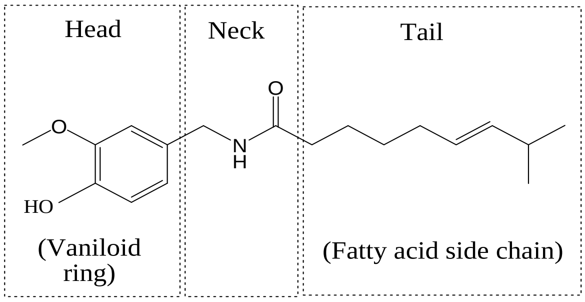
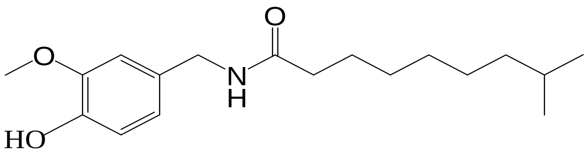
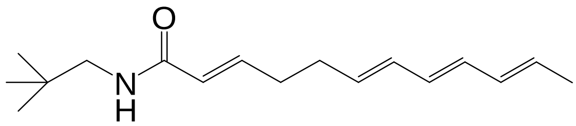
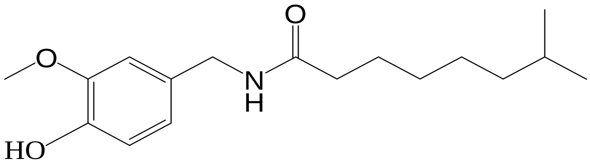
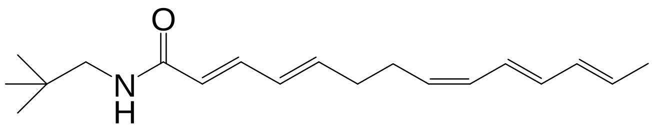
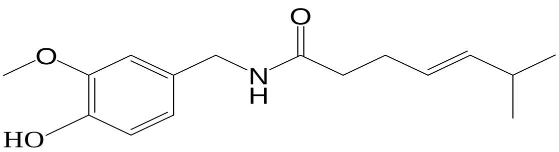
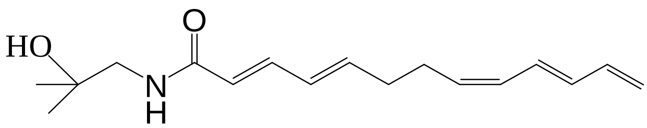
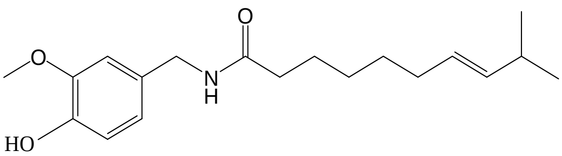
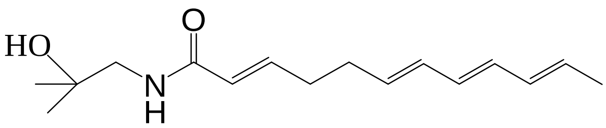
Sanshools	Capsaicinoids
 Capsaicin (Active component)	 α-Sanshool (Active component)
Other Capsaicinoids	**Other Sanshools**
 Dihydrocapsaicin	 B-Sanshool
 Nordihydrocapsaicin	 γ-Sanshool
 Nornohydrocapsaicin	 Hydroxyl-γ-Sanshool
 Homocapsaicin	 β-Sanshool

Table 1: Structural comparison of major sanshools and capsaicinoids

Structures were drawn by authors using ChemDraw Ultra 8.0

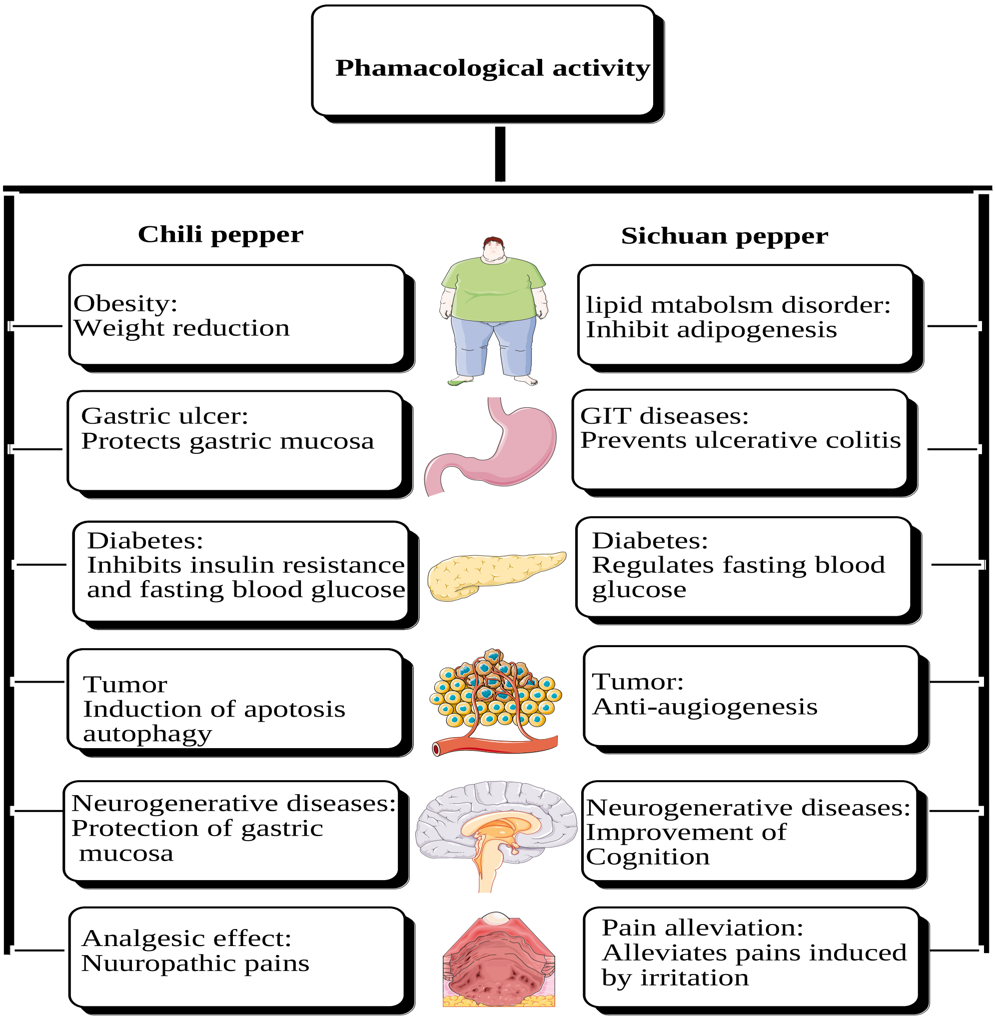


Figure 1: The comparison of pharmacological activities between Chili and Sichuan peppers

Figure was designed and drawn by authors.