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Title: The influences of thermal processing on phytochemicals and possible routes to the discovery of new phytochemical conjugates

Running title: Influences of thermal processing on phytochemicals

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Abstract:

In our diets, many of the consumed foods are subjected to various forms of heating and thermal processing. Besides enhancing the taste, texture, and aroma of the foods, heating helps to sterilize and facilitate food storage. On the other hand, heating and thermal processing are frequently reported during the preparation of various traditional herbal medicines. In this review, we intend to highlight works by various research groups which reported on changes in phytochemicals and bioactivities, following thermal processing of selected plant-derived foods and herbal medicines. Relevant cases from plant-derived foods (garlic, coffee, cocoa, barley) and traditional herbal medicines (*Panax ginseng, Polygonum multiforum, Aconitum carmichaelii* Debeaux, *Angelica sinensis* Radix) will be presented in this review. Additionally, related works using pure phytochemical compounds will also be highlighted. In some of these cases, the amazing formation of new compounds were being reported. Maillard reaction could be concluded as the predominant pathway leading to the formation of new conjugates, along with

other possibilities being suggested (degradation, transglycosylation, deglycosylation and dehydration). With collective efforts from all researchers, it is hoped that more details will be revealed and lead to the possible discovery of new, heat-mediated phytochemical conjugates.

Keywords: Maillard reaction, medicinal herb, plant-derived food, traditional medicine

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1. Introduction

Plants, rich with their diverse phytochemical groups such as phenolic compounds, provide us with essential nutrients and contribute to our overall health and well beings. These diverse phytochemical groups also represent a potent reservoir to explore for potentially useful bioactive compounds. In most places, plant-based foods contribute to a significant portion of the daily diets, which include but not limited to grains, fruits, vegetables, and beans. Likewise, many of the traditional medicines used across different cultures are derived from various parts of medicinal plants. In fact, some of our modern pharmaceutical drugs are originated from plants. Examples include chemotherapeutic vinblastine and vincristine, derived originally from *Catharanthus roseus* (Madagascar periwinkle), as well as paclitaxel derived from the bark of *Taxus brevifolia* (pacific yew tree) (Bhanot, Sharma, and Noolvi, 2011; Wong, Tan, and Chai, 2016). Research efforts are still on going to fully appreciate these plant-derived phytochemicals and phenolic compounds.

During the processing of plant-derived foods, various cooking methods were involved (baking, boiling, heating, steaming and stewing). These thermal processing help to enhance the texture, aroma, and taste of these plant foods. Similarly, thermal processing is frequently involved during the preparation of traditional herbal medicines. Numerous reported cases have highlighted on how thermal processing could influence the phytochemical contents, and sometime could alter the bioactivities, of these plant-derived foods. In some cases, the formation of new phytochemical conjugates were reported. It is believed that energy derived from these thermal processing help to overcome the energy barriers and hence facilitate the phytochemical transformations. Frequently, the observed thermal-induced change in phytochemical contents could be attributed to Maillard reaction (a chemical reaction between amino acids and reducing sugars); however, in other cases, chemical reactions such as degradation, transglycosylation, deglycosylation, dehydration, and oxidation were proposed. Yet, in the remaining cases, the reaction mechanism remains to be determined.

In the following sections in this review, relevant examples on how thermal processing could alter the phytochemical contents in plant-derived foods (garlic, coffee, cocoa and barley) will be presented. Selected examples on the effects of thermal processing involved during the preparation of traditional herbal medicines (*Panax ginseng*, *Polygonum multiforum*, *Aconitum carmichaelii* Debeaux and *Angelica sinensis* Radix) will be summarized and presented.

Additionally, related works using pure molecular and phytochemical compounds will also be highlighted (Figure 1).

2. Effects of thermal processing on plant-derived foods

Since ancient time, plant-derived foods represent the major sources of dietary intakes for human beings. The sources of these plant-derived foods are numerous, which could range from staple foods such as rice, wheat, corn, and potato to condiments such as assorted spices, herbs and mints. During the preparation and cooking of these plant-derived foods, various forms of thermal processing and heating are frequently involved, which in turn could lead to changes in their phytochemical contents as presented in the following section.

Garlic represents one of the most common condiments used in cooking and food preparation. Among the different garlic products, black garlic is a unique culinary ingredient, produced by subjecting raw garlic bulbs to heat treatment. Upon heat treatment of garlic bulbs at 70 °C for certain time duration, the formation of various 2-furomethyl-amino acids were recently reported. The formation of 2-furomethyl-lysine, 2-furomethyl-γ-aminobutyric acid, and 2-furomethyl-arginene were detected by ion-pair reversed-phase high-performance liquid chromatography (RP-HPLC) (Ríos-Ríos et al., 2018). Likewise, in a different study which monitored the thermal processing of black garlics, decrease in the fructan (polymer of fructose molecules) content was detected, accompanied by increase in the fructose content (Yuan et al., 2018). Concurrently, the contents of Maillard reaction intermediate products (fructose-proline, fructose-valine and fructose-leucine) were detected as firstly increased and then decreased (Yuan et al., 2018). It remains unclear if these intermediate products were degraded in the reverse reactions or progressed into other products. In a recent report which studied the compositional differences between fresh and black garlics, it was found that heat treatment significantly changed the contents of selected compounds, namely those of the amino acid family (lysine, arginine, citrulline, 4-guanidinobutanoic acid) and organosulfur compounds (diphenyl disulfide, thiacremonone), saccharides (tri-saccharide) and others (carnitine, 5′-butyrylphosphouridine) (Molina-Calle et al., 2017). Some of these changes could be attributed to Maillard reaction (amino acids, tri-saccharide) and degradation reaction (citrulline, 4-guanidinobutanoic acid); however, the exact biochemical pathway of other compounds remain to be determined. Notably, the increment of thiacremonoe in black garlic bears interesting healthcare-related significances, as this particular organosulfur compound had been linked with anti-obesity (Ban et al., 2012) and anti-cancer (Jo et al., 2014) bioactivities.

Coffee is an important global commodity. After roasting, the coffee beans could be further processed into assorted brewed coffee drinks. Many efforts have been focused on studying how the different roasting processes will affect the coffee's phytochemical contents and bioactivities. Several studies have reported on the increases in coffee extract's antioxidant activities, after roasting process, along with the formation of Maillard reaction products (MRPs) (Kocadağlı and Gökmen, 2016; Liang et al., 2016; Y. Liu and Kitts, 2011; Moreira et al., 2017; Sacchetti et al., 2009). Similarly, another study has elucidated on the antioxidant capacity of MRPs from roasted coffee, and this study suggested hydrogen atom transfer and single electron transfer as the antioxidant mechanism (Y. Liu and Kitts, 2011). Monitoring the coffee roasting process, a separate study also reported on the striking decrease of ions in the range of m/z 500-

600 in mass spectra, accompanied by an increase of peaks in the m/z 600-700 and 800-900 ranges (Rosa et al., 2016). This observed increase in abundance in the m/z 600-700 and 800-900 ranges were reportedly contributed by increase in the contents of diacylglycerols and triacylglycerols, respectively (Rosa et al., 2016). Previously, it was reported that increasing roasting degree led to the reduction in polyphenol contents, possibly due to degradation pathway (Sacchetti et al., 2009). A recent study reported on other possible fates of coffee phenolics upon heat processing. Using gas and liquid chromatography coupled to a mass spectrometry (GC-MS, LC-MS), this study reported on non-enzymatic transglycosylation reaction as a main mechanism for coffee phenolics to be incorporated into coffee melanoidins (a sugar-amino acid polymer produced by Maillard reaction)(Moreira et al., 2017). However, in this report, the bioactivity of this glycosidically-linked phenolic-melanoidin conjugates remains to be determined.

Cocoa is another important global commodity, whereby the cocoa beans are processed (fermenting, drying, roasting) into chocolate and cocoa powder products. Likewise, cocoa beans are also known to contain high amount of polyphenols. Previously, it was observed that during the drying and roasting processes, the polyphenol contents in cocoa beans were reduced, which may be attributed to degradation pathway during the thermal processing (Alean, Chejne, and Rojano, 2016). Concurrent study using liquid chromatography-mass spectrometry (LC-MS) method had also demonstrated on the reduction of phenolic compounds in cocoa beans, especially remarkable with respect to the epicatechin and procyanidin B2 contents (Żyżelewicz et al., 2016). Meanwhile, a separate study reported on how melanoidin-rich fraction (isolated from roasted cocoa brew) could inhibit against α-glycosidase, a potent enzyme target in the treatment of diabetes mellitus (Bellesia and Tagliazucchi, 2014). Likewise, various phenolic and phytochemical compounds had previously been reported with inhibition activities against α-glucosidase (Cao et al., 2017; Chai et al., 2015). As mentioned above, the content of cocoa phenolic compounds was decreased, following the thermal processing. However, it is still unclear if these cocoa phenolic compounds were merely degraded or conjugated into the cocoa melanoidins. Just as reported in the case of roasted coffee beans, it is likely that these cocoa phenolic compounds may be transglycosylated into the cocoa melanoidins, during the thermal drying and roasting processes. If this is indeed the case, then it is exciting to study whether these cocoa's phenolic-melanoidin conjugates demonstrate enhanced or totally new bioactivities.

Barley is a cereal grains used as human food, fermentation material in beer production, and as feed grain. Its nutritional value is cherished for the high contents of phytochemicals and β-glucan (a polysaccharide linked with cardiovascular health)(Sharma and Kotari, 2017). Before human consumption, barley is subjected to various processing steps (Sharma and Kotari, 2017). Previously, it was reported that following extrusion cooking process, the barley's total phenolic content and total flavonoid content were significantly reduced (Sharma, Gujral, and Singh, 2012). Upon thermal processing at 150 °C or 180 °C, barley extract demonstrated an enhanced antioxidant and metal chelating activities (Sharma, Gujral, and Singh, 2012). Amazingly, similar results were observed using different methods of thermal processing, such as sand roasting of barley (Sharma and Gujral, 2011). Additionally, barley melanoidins yielded from water cooking method was also reported with enhanced radical scavenging activity (Carvalho et al., 2014). From these barley-related reports presented here, the observed activity enhancements may likely be independent of the preparation methods. Instead, the heat-mediated thermal processing may be the key reason which trigger these changes in phenolic contents and activities. It is tempting to speculate that the reduced barley phytochemicals may be conjugated into the barley melanoidins, via similar transglycosylation reaction as observed with coffee melanoidins. However, more research is needed in order to determine the type of molecular conjugates being generated, as well as the accompanying mechanism.

3. Effects of thermal processing on traditional herbal medicines

Across different regions of the world, traditional herbal medicine is frequently resorted to for relieving of diseases and for maintaining of overall well-being. During the preparation of these medicinal herbs, thermal processing (boiling, drying, heating, steaming) is frequently involved. In some cases, the thermal processing seems to alter the herbal chemical components. New phytochemical conjugates were detected, which was absence prior to the thermal processing. The following section highlights some of these reported phenomenon observed in herbal extracts, following thermal processing.

Polygonum multiflorum (Heshouwu) is a popular Traditional Chinese Medicine (TCM) used for rejuvenative purposes. During the processing of *P. multiflorum,* steaming is frequently involved. Previously, it was reported that a new chromatographic peak was detected from the steamed *P. multiflorum* root extract, in a HPLC analysis (Z. Liu et al., 2009). Interestingly, the intensity of this new chromatographic peak increased proportionally with steaming times ranged 8-48 hours, and this new peak was not detected prior to the steaming. Later, the presence of 2,3-dihydro-3,5-dihydroxy-6-methyl-4(H)-pyran-4-one and 5-hydroxymethyl furfural were confirmed in this new chromatographic peak (Z. Liu et al., 2009). Likewise, in a subsequent study using steamed *P. multiflorum* extract, eleven new compounds were identified (four furanones, two furans, two nitrogen compounds, one pyran, one alcohol and one sulfur compound)(Z. Liu et al., 2011). Among these 11 newly formed products following steaming, 5-hydroxymethyl-furfural was further tested and demonstrated with potent radical scavenging activities (Z. Liu et al., 2011). In both studies, Maillard reaction was believed to involve in the formation of these new conjugates.

Panax ginseng is another traditional medicinal herb treasured as health promoting tonic. Traditionally, *P. ginseng* could be processed into white ginseng (sun-dried ginseng) or red ginseng (steaming fresh ginseng at 95-100 °C for a certain time duration), depending on the presence of this steaming step (Cho et al., 2008; Zhou et al., 2017). Previously, numerous studies had reported on *P. ginseng* rich phytochemical contents (Bezerra et al., 2016; Lee et al., 2015; Ma and Yang, 2015; Qiu et al., 2015; Wu et al., 2018; Zhu et al., 2011). Panaxydol, a member of polyacetylenes, is a phytochemical isolated from the root of *P. ginseng*. Recently, in a study employing ultra-performance liquid chromatography (UPLC) analytical approach, it was reported that following the steaming process, the steamed red ginseng possessed higher panaxydol content, compared to the un-steamed white ginseng sample (Zhou et al., 2017). This finding bears medicinal significance, as this small molecule had been reported with apoptotic bioactivity in a recent anti-cancer study (H. S. Kim et al., 2016). One suggested possible route for the formation of panaxydol is via the oxidation of panaxytriol, another polyacetylene, following the thermal processing (Zhou et al., 2017).

Besides panaxytriol, the effects of thermal processing on ginsenosides (major active components in *P. ginseng*) had also been investigated. Here, it was reported that upon thermal processing at 120 °C, four HPLC chromatographic peaks corresponding to ginsenosides (Rb_1, Rb_2, Rc and Rd) disappeared, while three new ginsenosides with lower polarity (Rg_3, Rk_1, Rg_5) were newly detected (Y. J. Kim et al., 2013). It was deduced that during the thermal processing, ginsenoside Rd could be transformed into ginsenoside Rg_3, possible via deglycosylation and dehydration pathways (Y. J. Kim et al., 2013). Tested on human gastric cancer AGS cell line, this same study also demonstrated ginsenoside Rg3 with increased anti-cancer activity.

An earlier study on *P. ginseng* reported on the decrease in its free amino acid content, following thermal processing. Notably, the content of arginine, a predominant amino acid in *P. ginseng*, was reduced by 86% (Cho et al., 2008). Likewise, the content of β-N-oxalyl-L-α,β-diaminopropionoic acid (β-ODAP, a naturally occurring non-protein amino acid) was greatly reduced. It was believed that the reduction in the free amino acids could be attributed to the formation of Maillard reaction products (MRPs). The MRPs formation may partly explain the enhanced radical scavenging activities observed in steamed *P. ginseng* extract, as a MRPs-rich fraction extracted from steamed *P. ginseng* was found with potent anti-oxidant activity (Cho et al., 2008). However, the β-ODAP transformation pathway remains unclear.

In traditional Chinese medicine (TCM), it is common to include the use of herb pair or herbal formula for treating diseases. In these TCM herb pair or herbal formula, two or more different medicinal herbs could be combined in different ratios and processed into a single decoction (Jin et al., 2016; Yang et al., 2014). It is believed that the combined herbs in an herbal formula could work synergistically and enhance the medicinal values. During the preparation of decoction from herbal formula, heating and boiling are usually involved. Previously, there were studies reported on the detection of new phytochemical conjugates in decoction derived from herbal formula. Interestingly, some of these new phytochemical conjugates were not detected in any of the single herb.

For example, it was reported that fifty chemical components were detected by gas chromatography-mass spectrometry (GC-MS) in the volatile oil prepared from herb pair *flos lonicerae-caulis lonicerae* (FL-CL). Among these fifty chemical components detected, ten of them are new chemical constituents which were not found in the volatile oil prepared from the single herb of FL or CL (Zhan et al., 2010). Similarly, in a separate HPLC study which compared decoctions derived from herb pair *Angelicae Sinensis* Radix-*Astragali* Radix (Danggui-Huangqi) and its single herb component, two new peaks were detected. These two peaks were attributed to new components found only in the herb pair decoction (Jin et al., 2016; Wang et al., 2005). Likewise, in a LC-MS comparative analysis between herb pair *Aconitum camichaelii* Debeaux-*Glycyrrhizae* Radix (Fuzi-Gancao) and its single herb decoction, differences in phytochemical contents were reported. Here, increases in diester-diterpenoid and alkylolamine-diterpenoid alkaloids, accompanied by decrease in monoester-diterpenoid alkaloids, were observed in the herb pair decoction (Yang et al., 2014). In these herb pair examples presented here, the underlying mechanism which leads to the differences in phytochemical contents between herb pairs and their single herbs remain unclear. It is tempting to speculate that part of the reason may be the formation of phytochemical conjugates through Maillard-like reactions or some other heat-induced transformation pathways.

4. Effects of thermal processing on pure molecular and phytochemical compounds

Aside from plant derived food and traditional herbal medicine examples, studies done using pure molecular compounds offer additional clues on the effects of thermal processing, as well as the possible routes which could lead to the generation of new molecular conjugates. Some of the examples presented here bear the characteristics of a Maillard reaction. For example, using mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopic methods, the production of 1-deoxyosone intermediate was confirmed, when 1-deoxymaltulosyl-glycine (glycyl-fructosyl-glucose) was heated at 100 °C, in the presence of cysteine (Ota, Kohmura, and Kawaguchi, 2006). Likewise, when pure tyrosine and fructose when subjected to 130 °C thermal processing mimicking a food model system, the formation of fructose-tyrosine Maillard reaction products (MRPs) was detected (Hwang et al., 2012). Additionally, 2,4-bis(p-hydroxyphenyl)-2-butenal (HPB242) was further purified and isolated from the fructose-tyrosine MRPs, followed by structural determination using NMR method. When tested in a MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) anti-proliferative assay, this HPB242 molecule demonstrated growth inhibitory activities against six selected human cancer cell lines (Hwang et al., 2012).

Moreover, other study reported on the thermal processing effect with rutin (a common phytochemical found in many medicinal herbs and edible plants). Following a heat-mediated reaction, a new rutin-lysine MRP conjugate was detected. Tested using HepG2 (human liver cancer cell line), this new rutin-lysine conjugate was reported with increased radical scavenging activity (Zhang et al., 2016). Likewise, this new rutin-lysine conjugate demonstrated higher antioxidant activities against Cu^{2+}-induced oxidative stress, compared to rutin (Zhang et al., 2016). Although the mechanistic detail remains unclear, the enhanced antioxidant potential may likely be mediated by increased superoxide dismutase's gene expression, as reported in this same study. On the other hand, ferulic acid is a member of hydroxycinnamic acids, and it is a phytochemical commonly found in many plants. When pure ferulic acid was subjected to thermal processing at 200 °C, in a glucose/ glycine simulated baking model, the formation of ferulic acid-MRP conjugate was detected using mass spectrometry (MS) and nuclear magnetic resonance (NMR) methods (Deshou et al., 2009). This ferulic acid-MRP conjugate was tested with the ability to suppress expression of nitric oxide synthase and cyclooxygenase, which are two enzymes involved in pro-inflammatory mechanism (Deshou et al., 2009). Surprisingly, no gene suppression was detected in the ferulic acid control. Just as observed in these cases presented here, the possibility for the formation of new phytochemical conjugates, following thermal processing, was highlighted. It would not be surprising when more of these phytochemical conjugates are reported with therapeutic related functionality in the future.

5. Concluding Remarks

From the examples on plant-derived foods, traditional medicines and pure compounds discussed above, the potential formation of new molecular conjugates, following thermal processing, is highlighted. Many of these reported molecular conjugates could be attributed as Maillard reaction products. Additionally, degradation, transglycosylation, deglycosylation, dehydration, and oxidation have also been proposed as possible transformation routes which could lead to the formation of these molecular conjugates.

Simply put, at least from the examples presented here, two basic pre-existing criteria need to be fulfilled before the detection of new molecular conjugate is possible: thermal processing (heating, boiling, roasting and stewing) and mixture of molecules (saccharides, amino acids, assorted phytochemicals). From the perspective of daily lives, these two criteria are frequently met during food preparation processes in the kitchen. Take, for example, the making of chicken soup seasoned with assorted spices, herbs, and mints. Besides enhancing the taste and aroma, could it be possible that the addition of these plant-based condiments helps to provide vast library of phytochemicals and small molecules which will interact and lead to the formation of health-promoting molecular conjugates? Likewise, from a more scientific oriented perspective, could it be possible that the presence or absence of thermal processing will directly affect the formation of therapeutic molecular conjugates? It is very likely, as thermal processing could provide extra kinetic energy for the molecules to overcome the activation energy barrier, and to progress toward the formation of molecular conjugates.

Lastly, many of the examples presented in this review focused on testing these thermal-induced molecular conjugates for their antioxidant, anti-cancer, anti-diabetic, and anti-inflammatory bioactivities. In the future studies, it would be interesting to determine if these molecular conjugates may possess other therapeutic potentials undiscovered yet, including but not limited to anti-viral, immunomodulation and anti-thrombotic potentials. Similarly, it is still unclear how these thermal-induced molecular conjugates would be metabolized when tested in animal models. Hopefully, with accumulated studies and collective efforts, more details could be revealed on the formation of thermal-mediated phytochemical conjugates and their corresponding bioactivities.

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References

Alean, J., Chejne, F., and Rojano, B. (2016). Degradation of polyphenols during the cocoa drying process. *Journal of Food Engineering*, ***189***, 99-105.

Ban, J. O., Lee, D. H., Kim, E. J., Kang, J. W., Kim, M. S., Cho, M. C., Jeong, H. S., Kim, J. W., Yang, Y., Hong, J. T., and Yoon, D. Y. (2012). Antiobesity Effects of a Sulfur Compound Thiacremonone Mediated via Down-regulation of Serum Triglyceride and

Glucose Levels and Lipid Accumulation in the Liver of db/db Mice. *Phytotherapy Research*, ***26***(9), 1265-1271.

Bellesia, A., and Tagliazucchi, D. (2014). Cocoa brew inhibits in vitro α-glucosidase activity: The role of polyphenols and high molecular weight compounds. *Food Research International*, ***63, Part C***, 439-445.

Bezerra, A. G., Negri, G., Duarte-Almeida, J. M., Smaili, S. S., and Carlini, E. A. (2016). Phytochemical analysis of hydroethanolic extracts from powdered roots of Panax ginseng C. A. Meyer and Heteropterys tomentosa A. Juss and evaluation of their effects on astrocyte cell death. *Quimica Nova*, ***39***(5), 581-587.

Bhanot, A., Sharma, R., and Noolvi, M. N. (2011). Natural sources as potential anti-cancer agents: A review. *International Journal of Phytomedicine*, ***3***(1), 09-26.

Cao, H., Chai, T. T., Wang, X., Morais-Braga, M. F. B., Yang, J. H., Wong, F. C., Wang, R., Yao, H., Cao, J., Cornara, L., Burlando, B., Wang, Y., Xiao, J., and Coutinho, H. D. M. (2017). Phytochemicals from fern species: potential for medicine applications. *Phytochemistry Reviews*, ***16***(3), 379-440.

Carvalho, D. O., Correia, E., Lopes, L., and Guido, L. F. (2014). Further insights into the role of melanoidins on the antioxidant potential of barley malt. *Food Chemistry*, ***160***, 127-133.

Chai, T. T., Kwek, M. T., Ong, H. C., and Wong, F. C. (2015). Water fraction of edible medicinal fern Stenochlaena palustris is a potent α-glucosidase inhibitor with concurrent antioxidant activity. *Food Chemistry*, ***186***, 26-31.

Cho, E. J., Piao, X. L., Jang, M. H., Baek, S. H., Kim, H. Y., Kang, K. S., Kwon, S. W., and Park, J. H. (2008). The effect of steaming on the free amino acid contents and antioxidant activity of Panax ginseng. *Food Chemistry*, ***107***(2), 876-882.

Deshou, J., Christopher, C., Pranav, M., Sandeep, K., and Peterson, D. G. (2009). Identification of hydroxycinnamic acid - maillard reaction products in low-moisture baking model systems. *Journal of Agricultural and Food Chemistry*, ***57***(21), 9932-9943.

Hwang, I. G., Kim, H. Y., Lee, S. H., Woo, K. S., Ban, J. O., Hong, J. T., Yu, K. W., Lee, J., and Jeong, H. S. (2012). Isolation and identification of an antiproliferative substance from fructose–tyrosine Maillard reaction products. *Food Chemistry*, ***130***(3), 547-551.

Jin, Y., Qu, C., Tang, Y., Pang, H., Liu, L., Zhu, Z., Shang, E., Huang, S., Sun, D., and Duan, J.-a. (2016). Herb pairs containing Angelicae Sinensis Radix (Danggui): A review of bio-active constituents and compatibility effects. *Journal of Ethnopharmacology*, ***181***, 158-171.

Jo, M., Yun, H. M., Park, K.-R., Park, M. H., Lee, D. H., Cho, S. H., Yoo, H. S., Lee, Y.-M., Jeong, H. S., Kim, Y., Jung, J. K., Hwang, B. Y., Lee, M. K., Kim, N. D., Han, S. B., and Hong, J. T. (2014). Anti-Cancer Effect of Thiacremonone through Down Regulation of Peroxiredoxin 6. *PLOS ONE*, ***9***(3), e91508.

Kim, H. S., Lim, J. M., Kim, J. Y., Kim, Y., Park, S., and Sohn, J. (2016). Panaxydol, a component of Panax ginseng, induces apoptosis in cancer cells through EGFR activation and ER stress and inhibits tumor growth in mouse models. *Int J Cancer*, ***138***(6), 1432-1441.

Kim, Y. J., Yamabe, N., Choi, P., Lee, J. W., Ham, J., and Kang, K. S. (2013). Efficient thermal deglycosylation of ginsenoside Rd and its contribution to the improved anticancer activity of ginseng. *Journal of Agricultural and Food Chemistry*, ***61***(38), 9185-9191.

Kocadağlı, T., and Gökmen, V. (2016). Effect of roasting and brewing on the antioxidant capacity of espresso brews determined by the QUENCHER procedure. *Food Research International*, ***89, Part 2***, 976-981.

Lee, D. G., Lee, A. Y., Kim, K. T., Cho, E. J., and Lee, S. (2015). Novel dammarane-type triterpene saponins from Panax ginseng root. *Chemical and Pharmaceutical Bulletin*, ***63***(11), 927-934.

Liang, N., Xue, W., Kennepohl, P., and Kitts, D. D. (2016). Interactions between major chlorogenic acid isomers and chemical changes in coffee brew that affect antioxidant activities. *Food Chemistry*, ***213***, 251-259.

Liu, Y., and Kitts, D. D. (2011). Confirmation that the Maillard reaction is the principle contributor to the antioxidant capacity of coffee brews. *Food Research International*, ***44***(8), 2418-2424.

Liu, Z., Chao, Z., Liu, Y., Song, Z., and Lu, A. (2009). Maillard reaction involved in the steaming process of the root of Polygonum multiflorum. *Planta Medica*, ***75***(1), 84-88.

Liu, Z., Liu, Y., Chao, Z., Song, Z., Wang, C., and Lu, A. (2011). In vitro antioxidant activities of Maillard reaction products produced in the steaming process of Polygonum multiflorum root. *Natural Product Communications*, ***6***(1), 55-58.

Ma, L. Y., and Yang, X. W. (2015). Six new dammarane-type triterpenes from acidic hydrolysate of the stems-leaves of Panax ginseng and their inhibitory-activities against three human cancer cell lines. *Phytochemistry Letters*, ***13***, 406-412.

Molina-Calle, M., de Medina, V. S., Priego-Capote, F., and de Castro, M. D. L. (2017). Establishing compositional differences between fresh and black garlic by a metabolomics approach based on LC–QTOF MS/MS analysis. *Journal of Food Composition and Analysis*, ***62***, 155-163.

Moreira, A. S. P., Nunes, F. M., Simões, C., Maciel, E., Domingues, P., Domingues, M. R. M., and Coimbra, M. A. (2017). Transglycosylation reactions, a main mechanism of phenolics incorporation in coffee melanoidins: Inhibition by Maillard reaction. *Food Chemistry*, ***227***, 422-431.

Ota, M., Kohmura, M., and Kawaguchi, H. (2006). Characterization of a new maillard type reaction product generated by heating 1-deoxymaltulosyl-glycine in the presence of cysteine. *Journal of Agricultural and Food Chemistry*, ***54***(14), 5127-5131.

Qiu, S., Yang, W.-z., Shi, X. j., Yao, C. l., Yang, M., Liu, X., Jiang, B. h., Wu, W. y., and Guo, D.-a. (2015). A green protocol for efficient discovery of novel natural compounds: Characterization of new ginsenosides from the stems and leaves of Panax ginseng as a case study. *Analytica Chimica Acta*, ***893***, 65-76.

Ríos-Ríos, K. L., Vázquez-Barrios, M. E., Gaytán-Martínez, M., Olano, A., Montilla, A., and Villamiel, M. (2018). 2-Furoylmethyl amino acids as indicators of Maillard reaction during the elaboration of black garlic. *Food Chemistry*, ***240***, 1106-1112.

Rosa, J. S. d., Freitas-Silva, O., Rouws, J. R. C., Moreira, I. G. d. S., Novaes, F. J. M., Azevedo, D. d. A., Schwab, N., Godoy, R. L. d. O., Eberlin, M. N., and Rezende, C. M. d. (2016). Mass spectrometry screening of Arabica coffee roasting: A non-target and non-volatile approach by EASI-MS and ESI-MS. *Food Research International*, ***89, Part 2***, 967-975.

Sacchetti, G., Mattia, C. D., Pittia, P., and Mastrocola, D. (2009). Erratum to “Effect of roasting degree, equivalent thermal effect and coffee type on the radical scavenging activity of coffee brews and their phenolic fraction" [J. Food Eng. 90 (2009) 74–80]. *Journal of Food Engineering, **91***(2), 372.

Sharma, P., and Gujral, H. S. (2011). Effect of sand roasting and microwave cooking on antioxidant activity of barley. *Food Research International, **44***(1), 235-240.

Sharma, P., Gujral, H. S., and Singh, B. (2012). Antioxidant activity of barley as affected by extrusion cooking. *Food Chemistry, **131***(4), 1406-1413.

Sharma, P., and Kotari, S. L. (2017). Barley: Impact of processing on physicochemical and thermal properties—A review. *Food Reviews International, **33***(4), 359-381.

Wang, Y. L., Liang, Y. Z., Li, B. Y., Hu, Y., and Hu, Q. N. (2005). Relative adscription of components between complex and single herb in Danggui Buxue Decoction. *Zhongcaoyao, **36***(1), 1457-1460.

Wong, F. C., Tan, S. T., and Chai, T. T. (2016). Phytochemical-mediated Protein Expression Profiling and the Potential Applications in Therapeutic Drug Target Identifications. *Critical Reviews in Food Science and Nutrition, **56***(sup1), S162-S170.

Wu, W., Jiao, C., Li, H., Ma, Y., Jiao, L., and Liu, S. (2018). LC-MS based metabolic and metabonomic studies of Panax ginseng. *Phytochemical Analysis, **Article in Press***.

Yang, Y., Yin, X. J., Guo, H.-M., Wang, R. L., Song, R., Tian, Y., and Zhang, Z.-J. (2014). Identification and comparative analysis of the major chemical constituents in the extracts of single Fuzi herb and Fuzi-Gancao herb-pair by UFLC-IT-TOF/MS. *Chinese Journal of Natural Medicines, **12***(7), 542-553.

Yuan, H., Sun, L., Chen, M., and Wang, J. (2018). An analysis of the changes on intermediate products during the thermal processing of black garlic. *Food Chemistry, **239***, 56-61.

Zhan, X. h., Xu, G.-w., Li, F., Li, X. r., Zhou, S. a., Cao, F., and Li, X. (2010). Comparative analysis of volatile constituents between herbal pair flos lonicerae-caulis lonicerae and its single herbs. *Journal of Central South University of Technology*, ***17***(4), 726-731.

Zhang, R., Zhang, B. L., He, T., Yi, T., Yang, J. P., and He, B. (2016). Increase of rutin antioxidant activity by generating Maillard reaction products with lysine. *Bioorganic & Medicinal Chemistry Letters*, ***26***(11), 2680-2684.

Zhou, S. S., Xu, J., Kong, M., Yip, K.-M., Xu, J. D., Shen, H., Zhao, Z.-Z., Li, S. L., and Chen, H.-B. (2017). Synchronous characterization of carbohydrates and ginsenosides yields deeper insights into the processing chemistry of ginseng. *Journal of Pharmaceutical and Biomedical Analysis*, ***145***, 59-70.

Zhu, G. Y., Li, Y. W., Hau, D. K. P., Jiang, Z. H., Yu, Z. L., and Fong, W. F. (2011). Protopanaxatriol-type ginsenosides from the root of Panax ginseng. *Journal of Agricultural and Food Chemistry*, ***59***(1), 200-205.

Żyżelewicz, D., Krysiak, W., Oracz, J., Sosnowska, D., Budryn, G., and Nebesny, E. (2016). The influence of the roasting process conditions on the polyphenol content in cocoa beans, nibs and chocolates. *Food Research International*, ***89, Part 2***, 918-929.

Figure Legends

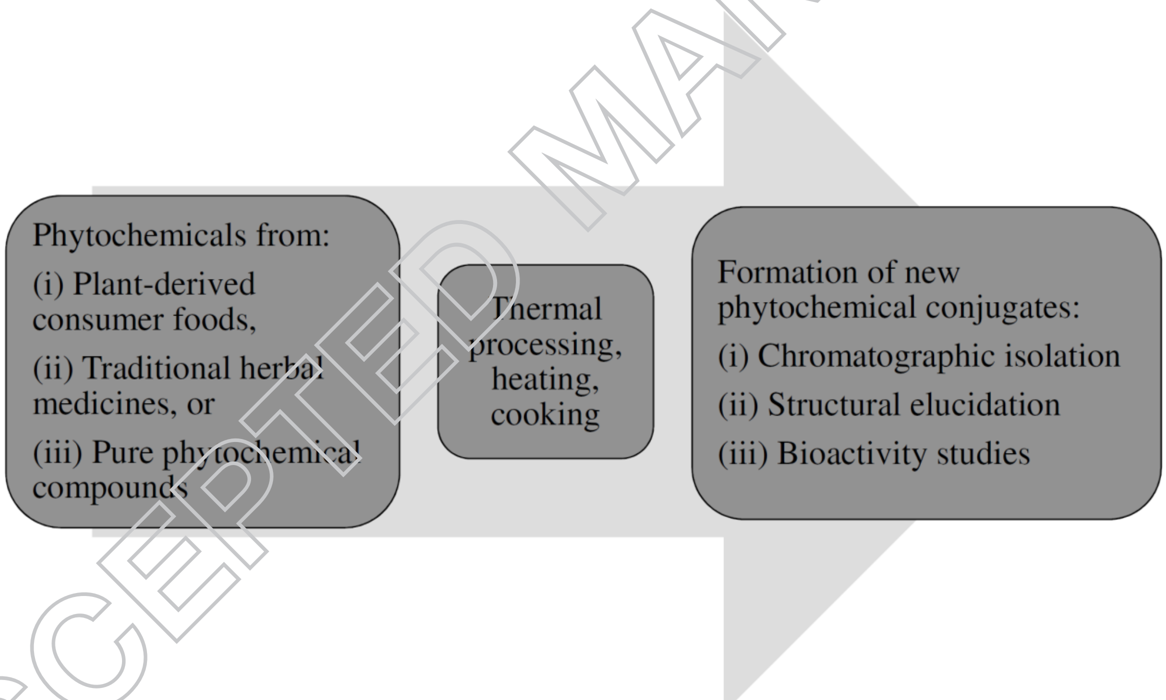

Figure 1. Different phytochemical sources and the studies on thermal-induced phytochemical conjugates.