http://dx.doi.org/10.4314/ajtcam.v12i2.9

HYDROXYMETHYL FURFURAL IN CHINESE HERBAL MEDICINES: ITS FORMATION, PRESENCE, METABOLISM, BIOACTIVITIES AND IMPLICATIONS

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Abstract

Background: Chinese herbal medicines (CHMs) must be processed before being prescribed to patients. During the processing, some CHMs became brown and as such 5-hydroxymethyl furfural (HMF) generated. Increasing attention is being paid to the safety and effectiveness of HMF.
Methods: This paper summarized previous and recent reports on HMF formation, its presence in CHMs, its metabolism and bioactivities, together with its implications for CHMs.
Results: HMF had been detected in 41 CHMs, and increased by about 12~1200 times after heat processing in some CHMs. Current data showed that HMF has limited genotoxicity but various bioactivities, such as anti-oxidative, anti-apoptotic, anti-inflammatory, anti-hypoxic, anti-microbial, and inhibiting sickling of red blood cells.
Conclusion: Accumulation of HMF during heat processing of CHMs indicates that Maillard reaction and caramelization occurred. The other products of the two browning reactions deserve more attention in the following investigations on heat processed CHM.

Keywords: hydroxymethyl furfural, Chinese herbal medicine, Maillard reaction, caramelization.

Introduction

Hydroxymethyl furfural (HMF) is a typical five-member heterocyclic organic compound with a formyl group and a hydroxyl methyl group. The generation of HMF is closely related to non-enzymatic browning reactions namely Maillard reaction and caramelization (Fadel and Farouk, 2002; Quintas et al., 2007). It was found widely present in sugar-containing processed foods/drinks, such as juice (Gökmen and Acar, 1999; Damasceno et al., 2008), honey (Spano et al., 2006), coffee (Murkovic and Bornik, 2007; del Campo et al., 2010; Arribas-Lorenzo and Morales, 2010), beverages (Monakhova and Lachenmeier, 2012; Maes et al., 2012), dried fruits (Murkovic and Pichler, 2006), cookies (Ameur et al., 2006) and bread (Ramirez-Jimenez et al., 2000; 2001). Its influence on food safety has raised wide concerns and its content has been used as an index for quality control of processed foods (Cohen et al., 1998; Zappala et al., 2005; Gaspar and Lucena, 2009).

In recent years, HMF has been frequently detected in Chinese herbal medicines (CHMs), especially, in processed CHMs. CHM processing, *Pao Zhi* in Chinese, is a pharmaceutical technology developed about 1000 years ago, aiming to eliminate non-medicinal substances, fit clinical application by cutting the crude materials into slices of desired size, diminish toxicity and side effects, moderate drastic actions, and enhance desired therapeutic effects. Methods of *Pao Zhi* are nearly all derived from cooking, including steaming, stewing, roasting, baking, calcining, and stir-frying with or without adjuvants (such as honey, rice wine, vinegar, ginger juice, bran, and bean curd) (Sionneau and Flaws, 1995). Since almost all these crude drugs and adjuvants contain sugars, amino acids, proteins and/or organic acids (Jia et al., 2002; Yang et al., 2008; Zhang et al., 2009), and most of these processing methods need high temperature, Maillard reaction and/or caramelization is unavoidable, leading to accumulation of HMF in the processed CHMs.

Up to now, remarkable progress has been made in studies on the biological activity, toxicity, formation and distribution of HMF in CHMs. This current paper reviewed related reports aiming to provide a better understanding of HMF in CHMs and its potential influence on the function and safety of CHMs.

Formation of HMF

Mechanisms of HMF formation

HMF is mainly generated by Maillard reaction and caramelization. Maillard reaction, namely amino-carbonyl reaction, refers to the reaction between compounds with amino groups and those with carbonyl groups that finally results in the accumulation of melanoids. HMF is an intermediate product of Maillard reaction. The early stage of Maillard reaction leads to the formation of Schiff's base with amino group (N-substituted glycosylamine) which is subsequently transformed into Amadori product. In the advanced stage, Amadori product breaks down by three routes among which the 3-deoxyosone-pathway (pH≤7) via the 1, 2 enolization leads to the formation of HMF (Hodge, 1953). In caramelization, HMF can be produced by direct dehydration of sugars like fructose and glucose, and the possible mechanism may involve two pathways: one is based on the changes of ring structure and the other occurs via simple acyclic compounds (Lewkowski, 2001). The former mechanism has been confirmed by experiments (Antal et al., 1990).

Intrinsic factors influencing HMF formation

HMF formation is closely related to the type of sugars that participate in the reaction. Generally the accumulation of HMF with sucrose being used as a substrate is apparently less than that with hexose such as fructose or glucose. However, when temperature reaches a high degree, sucrose begins to have a greater advantage as to the formation of HMF because it tends to be stable until the temperature increases to a high point, such as 300°C, at which complete hydrolysis of sucrose occurs. The fructose and glucose released during the hydrolysis of sucrose exhibit stronger activities than pre-existing hexoses in forming HMF (Ameur et al., 2007). The formation of fructofuranosyl cation from fructose was the first step in forming HMF (Roma´n-Leshkov et al., 2006). PerezLocas and Yaylayan found that 90% of HMF originated from fructose moiety of sucrose at temperatures above 250°C, however, when sucrose was refluxed in acidic methanol at 65 °C, 100% of HMF was generated from the glucose moiety. Under mild acidic conditions, glycosidic bond of sucrose can be easily cleaved to produce fructofuranosyl cation, and then HMF formed, however, it is much more difficult for the free fructose to generate the same cation (PerezLocas and Yaylayan, 2008).

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For hexoses, HMF formation from ketohexoses is faster than from aldohexoses. For example, fructose is superior to glucose in terms of reaction velocity. On one hand, the relative stability of the structure of glucose limits its enolization in a much greater degree, on the other hand, the oligosaccharides bearing reducing groups generated by the condensation of glucose will increase in proportions, and these newly produced oligosaccharides take part in further reactions with intermediates, such as HMF, which then gives rise to a cross-polymerization (Lewkowski, 2001). In addition, in aqueous solution the furan structure of fructose which can form fructofuranosyl cation under an acidic condition accounts for a large proportion and the furan rings of these fructofuranosyl cations then directly take part in HMF formation. By comparison, few furan structures exist in glucose, making the isomerization of glucopyranose to fructofuranose a need to form HMF. Apart from the transformation based on isomerization, glucose in certain proportion can be converted into HMF through 3-deoxyglucosone (3-DG), the intermediate formed from the open-ring structure of glucose (PerezLocas and Yaylayan, 2008). Because of the lower probability of glucose to exist in the form of open-ring as well as the complex side reactions of 3-DG, the speed of conversation into HMF is far behind that of fructose. Additionally, the formation of 3-DG usually needs amino compounds as catalysts, which is not for fructose.

Extrinsic factors influencing HMF formation

Except the intrinsic elements, the extrinsic ones such as temperature, acidity, water activity and some others also affect the production of HMF. For Maillard reaction and caramelization, temperature plays an important role in the reaction course (Ajandouz et al., 2008; Martins and Van Boekel, 2001). Usually the accumulation of HMF rises with the temperature increase, but the reverse may take place when the temperature increases to be quite high like 300°C. This can be ascribed to the degradation of HMF into secondary products such as furaldehyde and 2-methylfurfural (Ameur et al., 2008).

In a general way, lowering acidity enhances the propensity of HMF formation (Gökmen et al., 2007). In Maillard reaction, low pH facilitates the process of 1, 2-enolization of Amadori products which is the crucial step in forming HMF. Therefore from the perspective of Maillard reaction, acidic condition favors the formation of HMF. As for caramelization, it always takes place under a drastic condition such as more extreme pH (pH < 3 or > 9) (Kroh, 1994; Ajandouz et al., 2001). Wang et al. performed a study on the formation of HMF during heating treatment of the jujube juice and found that both strong acid and alkali accelerated the increase of HMF. When pH value was 6, the natural pH value for the jujube juice, the content of HMF was the lowest (Wang et al., 2011c).

Ameur et al. found that HMF content increased with water activity reduction from 0.4 to 0 (Ameur et al., 2006). The activation energy of HMF formation during pasteurization of apple cider (27.3 kJ/mol) (Gentry and Roberts, 2004) was much higher than that during baking cookies (10.63 kJ/mol) (Ameur et al., 2006). However, some literatures argued that HMF accumulation increased from dry state to a maximum at a water activity in the range of about 0.5-0.8 and then decreased at a higher water activity. A possible explanation for these changes was that higher water activity improved the mobility of solutes, leading to a higher reaction rate; and when water activity was up to 0.8, dilution effect on solutes became more significant and reduced the reaction rate (Vaikousi et al., 2008; Lavelli and Vantaggi, 2009), or water behaved as a reaction product and showed an inhibitory effect (Gögüs et al., 2000).

Some cations also influence HMF formation. Gökmen and Senyuva elucidated that Ca^{2+}, Mg^{2+}, and Fe^{3+} effectively boosted the accumulation of HMF by glucose-asparagines reaction model. They provided a reasonable explanation for this phenomenon by a chemical mechanism implying that these cations change the reaction pathway from the formation of Schiff base to the dehydration of glucose which leads to the increase of HMF (Gökmen and Senyuva, 2007). During the process of roasting cocoa, Oliviero et al. found that the presence of catechin obviously hindered HMF forming. “Carbonyl trapping” effect of catechin refers to the reaction between catechin and carbohydrates resulting in the generation of catechin-carbohydrate compounds. The formation of these adducts reduced carbohydrates or deoxyosuloses to the pathways that lead to HMF production (Oliviero et al., 2008). Additionally, leavening agents could also influence the formation of HMF by altering the degradation of sugars (Gökmen et al., 2008).

Some new methods for getting HMF from sugars

Rosatella has reviewed many synthetic methods of HMF (Rosatella, 2011). In recent years many new optimization methods have been applied to raise the production of HMF from sugars. Okano et al. established a recycled water/acetonitrile biphasic system induced by imidazolium chlorosulfate ($[MBCl_{10}]$ SO_3Cl) to accelerate the dehydration of fructose to HMF (Okano et al., 2013). Rajabbeigi et al. investigated different porous carbons as absorbents for selective removal of HMF from the well-known solvent dimethyl sulfoxide (DMSO) that allows for highly selective fructose dehydration to HMF (Rajabbeigi et al., 2012). Recently the selection of different catalysts as modifiers has been a hot research topic (Zhang et al., 2012b; Guan et al., 2011; Bali et al., 2012; Liu and Chen, 2013; Zhou et al., 2012a; Jadhav et al., 2012).

Presence of HMF in CHMs

HMF isolated from CHMs

HMF has been isolated and identified from a wealth of CHMs **(Table 1)**. The CHM materials used nearly all have been subjected to hot-air drying, and their isolation processes mostly undergo heat refluxing. However, whether HMF inherently exists in these CHMs and/or be newly produced in the process of drying and refluxing is still not clear.

HMF in processed CHMs

HMF is more often detected in CHMs that have been subjected to heat processing or prolonged storage. Generally speaking, the processing temperature and time, acidic conditions and the endogenous compounds such as fructose, organic acids or amino acids all exert influences on the generation and accumulation of HMF (Zhang et al., 2009). During steaming rehmannia root, HMF content increased concomitantly with the decrease of amino acids (Guo et al., 2012). Jia et al. have isolated and identified HMF from the sublimate of Cibot Rhizome and the source has been attributed to dehydration of glucose or fructose at high temperature (Jia et al., 2002). Yang et al. determined HMF in different processed products of *Polygonatum* and deemed that HMF was mainly derived from dehydration of reducing sugars or other polysaccharose (Yang et al., 2008). The existence of fructose, some proteins and amino acids as well as the prolonged storage can remarkably increase HMF contents in honey (Lu et al., 2006; Morales et al., 2009).

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Table 1: CHMs containing HMF

Origin	Materials	Detection methods	References
Aucklandia lappa DC. [*Saussurea lappa* C.B Clarke]	root slice	^{1}H-NMR	Yin et al. (2005)
Polygonatum odoratum (Mill.) Druce	rhizoma	^{1}H-NMR, ^{13}C-NMR	Li et al. (2010)
Citrus maxima (Burm.) Merr.	fruit peel	^{1}H-NMR	Feng and Pei (2000)
Stellaria dichotoma L. var. *lanceolata* Bge.	root	EI-MS, ^{1}H-NMR ^{13}C-NMR	Sun et al. (2006)
Urtica angustifolia Fisch. ex Hornem.	aboveground parts	EI-MS, ^{1}H-NMR IR, ^{13}C-NMR	Li et al. (2008)
Smilax glabra Roxb.	rhizoma	^{1}H-NMR, ^{13}C-NMR	Yuan et al. (2004)
Bolbostemma paniculatum (Maxim.) Franquet	bulb	^{1}H-NMR TLC	Zheng et al. (2005)
Liquidambar orientalis Mill.	resin	^{1}H-NMR	Wang et al. (2011a)
Rosa bracteata J. C. Wendl. [*Rosa bracteata* Wendl. var. *bracteata*.]	fruit	^{1}H-NMR, ^{13}C-NMR, MS, IR, UV	Yuan and Du (2000)
Acorus calamus L. var. *angustatus* Besser [*Acorus tatarinowii* Schott]	rhizoma	^{1}H-NMR, ^{13}C-NMR	Tong and Cheng (2011)
Elaeagnus rhamnoides (L.) A.Nelson [*Hippophae rhamnoides* L.]	fresh fruit	^{1}H-NMR	Dang et al. (2007)
Sparganium stoloniferum (Buch.-Ham. ex Graebn.) Buch.-Ham. ex Juz. [*Sparganium stoloniferum* Buch.-Ham.]	tuber	ESI-MS, ^{1}H-NMR, ^{13}C-NMR	An et al. (2009)
Millettia specisoa Champ.	root	ESI-MS, ^{1}H-NMR, ^{13}C-NMR	Wang et al. (2008)
Descurainia sophia (L.) Webb ex Prantl	seed	^{1}H-NMR, ^{13}C-NMR	Sun et al. (2005)
Ranunculus ternatus Thunb.	tuberous root	ESI-MS ^{1}H-NMR, ^{13}C-NMR	Chen et al. (2005)
Ophiopogon japonicus (Thunb.) Ker Gawl. [*Ophiopogon japonicus* (L. f.) Ker-Gawl.]	tuberous root	^{1}H-NMR, ^{13}C-NMR	Wang et al. (2009b)
[*Zantedeshia aethiopica* (L) Spreng]	herb	UV, GC-MS, ^{1}H-NMR, IR	Yang et al. (2009)
Humulus scandens (Lour.) Merr.	herb	ESI-MS, ^{1}H-NMR, ^{13}C-NMR	Cao (2012)
Pyrola calliantha Andres [*Pyrola calliantha* H. Andres]	herb	ESI-MS, ^{1}H-NMR, ^{13}C-NMR	Ren et al. (2010)
Euphorbia hylonoma Hand.-Mazz.	root	^{1}H-NMR, ^{13}C-NMR	Guo et al. (2007)
Carthamus tinctorius L.	tubular petal	^{1}H-NMR, ^{13}C-NMR	Zhou et al. (2007)
[*Cynanchum amplexicaule* Sieb. et Zucc.]	root and rhizoma	^{1}H-NMR, TLC	Chen et al. (2008)
Drynaria roosii Nakaike [*Drynaria fortune* (Kunze) J. Sm.]	rhizoma	^{1}H-NMR	Shang et al. (2010)
Heterosmilax yunnanensis Gagnep.	rhizome slice	^{1}H-NMR	Qin et al. (2007)
Cremastra appendiculata (D. Don) Makino	pseudobulb	^{1}H-NMR, ^{13}C-NMR	Zhang et al. (2007)
Sauromatum giganteum (Engl.) Cusimano & Hett. [*Typhonium giganteum* Engl.]	corm	^{1}H-NMR, ^{13}C-NMR	Shi et al. (2010) Zhang et al. (2010)
Clematis terniflora var. *manshurica* (Rupr.) Ohwi [*Clematis manshurica* Rupr.]	root and rhizoma	EI-MS, ^{1}H-NMR, ^{13}C-NMR	Shi et al. (2007)
Angelica acutiloba (Siebold & Zucc.) Kitag.	root	EI-MS, IR, ^{1}H-NMR, ^{13}C-NMR	Liu et al. (2011)
Hordeum vulgare L.	malt	^{1}H-NMR, TLC	Ling et al. (2005)
Melia azedarach L. [*Melia toosendan* Sieb. et Zucc.]	fruit	ESI-MS, ^{1}H-NMR	Xie et al. (2008)
Pinellia ternata (Thunb.) Makino [*Pinellia ternata* (Thunb.) Breit.]	corm	EI-MS, ^{1}H-NMR, ^{13}C-NMR	Yang et al. (2007)
Castanea mollissima Blume	seed	^{1}H-NMR	Zhang et al. (2008a)
Isatis tinctoria L. [*Isatis indigotica* Fort.]	root extract	TLC	Liu et al. (2002)
Atractylodes lancea (Thunb.) DC. [*Atractylodes chinensis* (DC.) Koidz.]	rhizoma slice	^{1}H-NMR, TLC	Li et al. (2003)
Coniogramme japonica (Thunb.) Diels	root and rhizoma	EIS-MS, ^{1}H-NMR	Fang et al. (2010)
Sinopodophyllum hexandrum (Royle) T.S.Ying [*Sinopodophyllum emodi* (Wall. Ying.]	root and rhizoma	^{1}H-NMR, ^{13}C-NMR	Sun et al. (2012)
Inula racemosa Hook. f.	root	EIS-MS, ^{1}H-NMR	Zhang and Chen (2011)

The names of plants have recently been accepted according to the website of The Plant List, and the names within square brackets are derived from original reports.

Apart from the factors mentioned above that affect contents of HMF in CHMs, different processing methods also influence HMF contents. HMF in steamed fruit of *Cornus officinalis* was more than the one pretreated with rice wine (Du et al., 2008). For the fruit of *Ligustri lucidi*, HMF content in the water-steamed sample was higher than the wine-steamed sample, but lower than the wine-stewed one (Cao et al., 2009). Rice wine, vinegar and honey can indirectly increase the content of HMF as they contain certain amounts of HMF (Theobald et al., 1998; Chen and Huang, 2010; Chen et al., 2009; Zhou et al., 2012b). Zhang et al. reported that HMF content in fried coix seeds without adjuvants was only about 7 times the amount of that in crude sample, while in bran fried coix seeds HMF content increased by 30 times, which was ascribed to Maillard reaction between sugars and amino acids in wheat bran (Zhang et al., 2012a). Overall, due to the existence of sugars and amino acids in CHM, heat treatment at a high temperature for a longer time will greatly contribute to the formation of HMF.

http://dx.doi.org/10.4314/ajtcam.v12i2.9

Metabolism of HMF

HMF could be readily absorbed from gastrointestinal tract in rats and mice (Godfrey et al., 1999), and HMF that was left unabsorbed could be transformed by enteric bacterial strains to 5-hydroxymethylfurfuryl alcohol, an intermediate metabolite (Boopathy et al., 1993). As such, toxicity caused by HMF may be reduced to a great extent as enteric bacteria can tolerate a higher concentration of 5-hydroxymethylfurfuryl alcohol. Godfrey et al. demonstrated that HMF could be metabolized rapidly in liver and kidney and excreted primarily via urine in rats and mice, and the majority of metabolites excreted was 5-hydroxmethyl-2-furoic acid (HMFA) followed by much lesser proportions of 2,5-furan dicarboxylic acid (FDCA) and N-(5-hydroxymethyl-2-furoyl) glycine (HMFG) (Godfrey et al., 1999). In human body, HMFA excreted via urine has been demonstrated to correlate well with HMF intake from food (Husøy et al., 2008). Jobstl et al. analyzed three hundred urine samples and showed that the concentration of HMFA in urine varied from 0 to 100 mg/L among which the majority was around 10 mg/L (Jobstl et al., 2010). Apart from HMFA, FDCA and HMFG have also been detected in human urine (Pettersen and Jellum, 1972). In addition, HMF can also be metabolized to sulfooxymethylfurfural (SMF), which has been proven to induce genotoxicity (Monien et al., 2009).

Bioactivities of HMF

For a long time, whether HMF is beneficial (a “friend”) or harmful (a “foe”) to human health has been a matter of debate. While HMF is still regarded as a strictly controlled ingredient in many foods (Cohen et al., 1998; Zappala et al., 2005; Gaspar et al., 2009), a growing number of studies have demonstrated that HMF is an active constituent in some CHMs. For instance, HMF was proven to be the main active component in steamed rehmannia root to improve erythrocyte deformability (Matsuda et al., 2004) and shown to play an important role in the anti-tumor metastasis property of *Ardisia crenata* (Wang et al., 2011). In addition, many beneficial effects of *Fructus corni* were also considered to be related to HMF (Ding et al., 2010; Wang et al., 2010; Zhang et al., 2008).

Anti-oxidative and anti-apoptotic activity

Oxidative stress appears when the balance between generation and elimination of reactive oxygen species (ROS) is disturbed. Production of ROS including free radicals and peroxides is a destructive aspect of oxidative stress. Severe oxidative stress can trigger cell apoptosis (Verhaegen et al., 1995) and necrosis. Many enzymes in a living body are positive cellular antioxidants, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px).

HMF was shown to alleviate high fat diet-induced oxidative damage to plasma and liver of mice by maintaining the levels of blood lipids, CAT, GSH-Px and reducing levels of ROS and malonaldehyde (Song et al., 2010). Additionally, HMF attenuated hydrogen peroxide-induced hippocampal neuronal injury, reducing the activity of lactic dehydrogenase and increasing that of SOD (Gu et al., 2011a). Similarly, due to the ability of reducing free radical levels and enhancing activity of SOD, HMF prolonged the survival of mice with permanent forebrain ischemia (Ya et al., 2012) and improved dysmnesia induced by cerebral ischemia and reperfusion (Zhang et al., 2007). In an *in vitro* study, Sharma et al. verified the antioxidative activity of HMF in suppressing tyrosinase in mushroom *Dictyophora indusiata* (Sharma et al., 2004).

As a potent antioxidant, HMF can resist oxidative stress-induced apoptosis. HMF prevented high glucose-induced oxidative stress in human umbilical vein endothelial cells mainly by rapidly balancing the levels and functions of the apoptosis-related Jun N-kinase1, Jun N-kinase2/3, plasma interleukin-8 (IL-8), phosphorylated protein kinase B (p-Akt) and ROS (Cao et al., 2013). HMF was considered to be an active component of processed *Fructus corni* for its protection of human LO2 hepatocytes from hydrogen peroxide injury-induced cell morphological change (Wang et al., 2010) and apoptosis (Ding et al., 2010), through its action in maintaining the cell cycle and in reducing nitric oxide release and activity of caspase-3 (Ding et al., 2010).

Pro-inflammatory or anti-inflammatory effect

Inflammation is part of complex biological responses of various tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammatory mediators derived from cells such as prostaglandin (PG) (Humes et al., 1977), nitric oxide (NO) (Kröncke et al., 1998), tumor necrosis factor-alpha (TNF-α) (Balkwill and Mantovani, 2001) and IL-8 (Baggiolini and Clark-Lewis, 1992) play significant roles in regulation of inflammatory responses. Uncontrolled inflammation can lead to tissue damages and are often involved in many immune system diseases, like allergic reaction (Galli et al., 2008) and some myopathies.

HMF isolated from *Litchi chinensis* was found to moderately stimulate the release of PGE_2 and NO in murine J774 macrophages by activating nuclear factor kappa B (NF-κB, a transcription factor known extensively involved in inflammation) and promoting mRNA expression of cyclooxygenase-2 (an enzyme responsible for PG formation) and inducible nitric oxide synthase (iNOS) (an enzyme catalyzing production of NO) (Zhou et al., 2012c). Whilst this finding suggests the potential pro-inflammatory effect of HMF, more reports have indicated the anti-inflammatory effect of HMF. Kim et al. found that HMF could significantly suppress the protein and mRNA expression of vascular cell adhesion molecule-1 and intercellular cell adhesion molecule-1 in TNF-α stimulated human umbilical vein endothelial cells by inhibiting NF-κB activation and production of ROS (Kim et al., 2011). In addition, HMF was identified as a potent inhibitor of xanthine oxidase, which interacts with Toll-like receptor-4 and leads to activation of NF-κB and then production of NF-κB dependent proinflammatory cytokines including TNF-α and macrophage inhibitory protein-2 (Lorne et al., 2008; Lin et al., 2012). Du et al. reported that HMF and its derivatives could significantly inhibit TNF-α or IL-1β expression (Du et al., 2005). Kitts et al. also proved that HMF could suppress the expression of iNOS, IL-8 and other related genes in cultured human colorectal adenocarcinoma cells by down-regulating NF-κB (Kitts et al., 2012). Furthermore, HMF exhibited anti-allergic effect by inhibiting the β-hexosaminidase (a chemical mediator) release at antigen-antibody binding stage and antibody-receptor binding stage (Yamada et al., 2011). Since ROS participates in inflammatory responses such as influencing NF-κB and up-regulating cell adhesion molecules (Vorbach et al., 2003), the ROS scavenging activity of HMF also supports its anti-inflammatory effects.

Anti-hypoxic effect

Hypoxic injures appear when oxygen supply is insufficient for the body or regions of the body. While rapid or severe hypoxia can result in detrimental events including coma, seizure, loss of consciousness and death, a hypoxic environment such as high altitude can cause maladaptive responses leading to various forms of acute altitude illness, such as acute mountain sickness, high altitude cerebral oedema and high-altitude pulmonary oedema (Wilson et al., 2009). Interestingly, the survival time and survival rate of mice exposed to acute hypobaric hypoxic condition

http://dx.doi.org/10.4314/ajtcam.v12i2.9

Table 2 Effects of processing temperature and time on HMF accumulation in CHMs (mg·kg^{-1})

Samples	Processing methods	Temperature (°C)	Heating time (h)												References
			0	4	8	9	10	16	24	32	40	48	52	72	
Linden honey	Heating	30	67.45	67.45	67.45			67.43	67.44						Zeng et al. (2002)
		80	67.45	180.45	248.56			503.97	785.5						
Buckwheat honey	Heating	90	4.19	> 100	> 600		>1000								Lu et al. (2006)
Chinese date honey	Heating	40	8.98	9.58	9.73		9.73								Zeng et al. (2006)
		80	8.98	31.1	77.89		140.1								
Rehmanniae radix	Steaming	100	200	400	900			1300	3500	4300	5600	6800	5700		Li et al. (2005)
		100	100		900			1490							Liu et al. (1995)
		130 (140Kp)	100		5360			11040							
		100	4.8	54.9	96.3			542.9	1719.2	2988.9	4216.1	5308.1	5625.9		Guo et al. (2012)
Polygoni multiflori radix	Stewing with fermented soya-bean milk	100			38			136	407	653	973	1710			Liu et al. (2008)
	Steaming	100								475.3	681.6			895.6	Chen et al. (2012)
Scrophulariae radix	Steaming	100	300			6600									Cao et al. (2012)

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were increased by pretreatment with HMF, as it ameliorated acute hypobaric hypoxia-induced permeability of blood-brain barrier and the extents.of cellular damage in the hippocampus and the cortex (Li et al., 2011a). While hypoxia is known to induce decline in mitochondria membrane potential (MMP) (Seol et al., 2009; Wang et al., 2009a), cell necrosis/apoptosis (Saikumar and Venkatachalam, 2003) and activation of extracellular signal-regulated kinase (ERK) (Mishra et al., 2004), HMF was found to attenuate hypoxic injury by effectively suppressing the decline of MMP and the ERK phosphorylation (Li et al., 2011b). In addition, HMF could increase tolerance to normobaric severe hypoxia without an adaptation process by enhancing hemoglobin O_2 affinity and improving hemodynamics and oxygenation (Yalcin and Cabrales, 2012).

Inhibiting sickling of red blood cells

Sickle-cell disease is a blood disorder characterized by the sickle shape of red blood cells and is caused by a mutation of hemoglobin gene. Due to the fact that heterocyclic aldehydes are prone to form Schiff base adducts with the N-terminal αVal1 nitrogens of hemoglobin (Zaugg et al., 1997), five-member heterocyclic aldehydes can bind to and stabilize the relaxed state hemoglobin; and they can also bind to and destabilize the tense state hemoglobin and then inhibit red cell sickling by allosterically shifting oxygen equilibrium curves toward the left (Safo et al., 2004). HMF possesses the structural basis for the above bindings and thus can be regarded as candidates for therapy of sickle cell disease. Pretreatment of transgenic sickle mice with HMF was found to remarkably inhibit formation of sickle cells and no adverse effects were detected on red blood cells (Abdulmalik et al., 2005). Binding of HMF to hemoglobin was found to not only increase the oxygen affinity of both normal and sickle hemoglobin but also to inhibit polymerization and formation of fibrous precipitates of the sickled hemoglobin (Lin et al., 2008). Moreover increased hemoglobin-oxygen affinity seemed to yield improved microvascular function and optimize the overall process of oxygen delivery by performing targeted oxygen delivery, preferentially releasing oxygen in regions with low P_{O2} and bypassing delivery to oxygenated areas (Villela et al., 2009). The above studies have indeed indicated the strong potential of HMF for treating sickle cell anemia, and currently it is used in clinical trials (Lin et al., 2008).

Anti-microbial effects

For a long time, the adverse effects of HMF on the growth of microorganisms have been noticed. HMF has been confirmed as one of active constituents in Thompson seedless raisins for restraining *Streptococcus mutans* and *Porphyromonas gingivalis*, two oral pathogens associated with caries and periodontal disease (Rivero-Cruz et al., 2008). As such, antibacterial compounds derived from plants have been suggested as alternative options or may be a better choice for dental plaque and oral disease control when compared to commonly used chemicals. In addition, due to its ability of inhibiting the three important metabolism enzymes (alcohol dehydrogenase, aldehyde dehydrogenase and pyruvate dehydrogenase) (Modig et al., 2002), HMF was found to inhibit the fermentation of *Saccharomyces cerevisiae* and itself was primarily converted into 5-hydroxymethylfurfuryl alcohol (Taherzadeh et al., 2000; Modig et al., 2002; Akıllıoglu et al., 2011). Consistently, glucose consumption as well as ethanol yield dramatically declined in the presence of HMF at concentrations at 1g/L or higher during fermentation of yeast (Wikandari et al., 2010). In view of the undesired inhibitory actions of HMF during bioethanol or biofuel fermentation production process, more tolerant yeast strains have been screened for the fermentation procedures (Liu et al., 2005). Sehnem *et al*. found that HMF could increase the expression levels for genes ADH7 and ARI1 in *Saccharomyces cerevisiae* strain P6H9 which was supposed to be responsible for the strong tolerance to HMF during bioethanol production (Sehnem et al., 2013).

Carcinogenic or Anti-carcinogenic action

Some Maillard reaction products (MRPs) are known to enhance the proliferation of human tumor cells, and there also exist some MRPs which bring about quite opposite effect (Marko et al., 2002; 2003). As one of MRPs, the carcinogenicity of HMF has long caused a quite stir in the research fields. Acher et al. reported that HMF consumption was associated with the increased occurrence of azoxymethane-induced aberrant crypt foci and microadenoma in the colon of treated rats (Acher et al., 1992). Similarly, Svendsen et al. found HMF increased the number of small adenomas in the intestine of *Min*/+ mice (Svendsen et al., 2009). On the contrary, Groke et al. invented an agent containing HMF that had a destructive effect on malignant tumors (Groke et al., 2010). Wang et al. isolated HMF from *Ardisia crenata* and found its inhibitory effect on tumor metastasis (Wang et al., 2011d). Some desirable therapeutic outcomes of HMF have also been reported in hormone-refractory and chemoinsensitive metastatic cancer (Michail et al., 2007). In addition, HMF was found selectively inhibiting the activities of mammalian DNA polymerase λ and terminal deoxynucleotidyltransferase *in vitro* (Mizushina et al., 2006). While some antitumor drugs targeting to DNA polymerase have been screened (Li et al., 1993), further studies could potentially explore the ability of HMF inhibiting DNA polymerase for the possibility of cancer treatment.

Improvement of learning and memory

The neural damage at the hippocampus (a brain region known involved with learning and memory function) is an important cause for the deterioration of learning and memory function of senile bodies. Zhang and Jin reported that HMF in *Rehmannia glutinosa* could protect hippocampal neurons against corticosterone-induced injuries by up-regulating the expression of glucocorticoid receptor (GCR), brain-derived neurotrophic factor (BDNF) and glucocorticoid-regulated protein kinase (SGK) (Zhang and Jin, 2012). Gu et al. found that HMF in processed *Fructus corni* could restrain the apoptosis of cultured hippocampal neurons by increasing the expression of B-cell lymphoma 2 (Bcl-2, an anti-apoptotic molecule) and decreasing the expression of NF-κB (Gu et al., 2011b). These studies suggest that HMF may likely to play an advantageous role in reinforcing learning and memory or reducing their impairment.

Genotoxicity

Given the presence of HMF in the processed foods and CHMs, potential genotoxicity of HMF has widely raised safety concerns. In recent years, while extensive work has been done investigating the genotoxicity of HMF, data are always inconsistent.

The genotoxicity of HMF was regarded to be activated by sulfotransferase (SULT1A1) (Glatt et al., 2005), which is expressed widely (Alnouti and Klaassen, 2006), especially in liver (Glatt and Meinl, 2004). SULT1A1 can promote the transformation of HMF into SMF, a compound capable of inducing gene mutations via binding with DNA to form adducts (Surh and Tannenbaum, 1994; Monien et al., 2009). Monien et al.

http://dx.doi.org/10.4314/ajtcam.v12i2.9

have further identified the DNA adducts as N^6-((2-formylfuran-5-yl)methyl)-2' -deoxyadenosine and N^2-((2-formylfuran-5-yl)methyl)-2'-deoxyguanosine, although these adducts could not be detected until 200 mM HMF was used (Monien et al., 2012). However, Durling et al. reported that the genotoxicity of HMF was not correlated with the activity of SULT1A1 as 100 mM HMF induced the most prominent DNA damage in cell lines with the lowest activities of SULT1A1 (L5178Y and Caco-2) but otherwise induced the lowest level of DNA damage in cell lines with the highest activity of SULT1A1 (HEK293) (Durling et al., 2009).

DNA damage can be reflected by SOS response in which the cell cycle is arrested and DNA repair and mutagenesis are induced. Assessment on SOS response by the umu assay (Umu Chromotest) in *Salmonella typhimurium* TA1535/pSK1002 in presence of HMF indicated that the genotoxicity of HMF (≥12 mM) was fairly low (Janzowski et al., 2000). By the Salmonella microsome assay, examination of possible mutagenic effects of HMF on the *Salmonella typhimurium* indicator strains TA98 and TA102 revealed the lack of obvious mutagenicity of HMF (Cheriot et al., 2009). Severin et al. used five strains including four *Salmonella typhimurium* strains and *Escherichia coli WP2uvrapKM101* to test the genotoxicity of HMF and found no genotoxic potential of HMF at the highest concentration (5000μg/plate) (Severin et al., 2010). They also tested the genotoxicity of HMF by hepatocellular carcinoma (HepG2) cells and found that HMF induced DNA damage at concentrations from 7.87 to 25 mM in comet assay (Severin et al., 2010). The discrepancy between these results may be attributed to the involvement of SULT1A1 in HepG2 cells. These studies suggest that, depending on cells and assays used, potential genotoxicity effect of HMF is inconsistent.

Other activities

Apart from those mentioned above, HMF also exhibits some other activities. For example, HMF can effectively protect nerve cells against injury induced by sodium azide (Zhang et al., 2008c) and okadaic acid (Zhang et al., 2008b) due to its ability to reduce β-amyloid (Aβ) build-up and protect cytoskeleton system. It has been reported that HMF can also inhibit the accumulation of lipid in mouse 3T3-L1 preadipocyte cells (Matsuda et al., 2006). HMF was also identified as the active constituent in *Acori tatarinowii* to effectively relieve fatigue (Zhu et al., 2012). Hou et al. found that HMF could significantly enhance the absorption of glycyrrhetic acid, a metabolite of glycyrrhizin and a chief constituent of *Glycyrrhiza glabra* (liquorice) root (Hou et al., 2005). Furthermore, Miyazawa et al. demonstrated that HMF had strong insecticidal activity against larvae of *Drosophila melanogaster* (Miyazawa et al., 2003).

Conclusion and implications of HMF in CHMs

In conclusion, HMF is widely distributed in CHMs, especially in those heat processed ones due to Maillard reaction and/or caramelization. According to the available data, its toxicity can be considered to be limited at currently prescribed dosages, and its various bioactivities are undeniable. However, whether HMF is responsible for the newly generated functions in the processed CHMs still remains largely unknown. In addition, while HMF is merely an intermediate formed out of these two complicated reactions, none of its end products melanoids have been characterized in CHMs up to now (Wang et al., 2011b), beneficial effects of melanoids have been well documented (Rufián-Henares et al., 2007a; 2007b; 2008; 2009; Wang et al., 2011b). It is possible that melanoids may be more important than HMF in mediating the newly formed actions for processed CHMs, a possibility that requires future investigations.

Although the doctrines of CHM processing are not only elusive to Western world but also to most Chinese as they were formed about 1000 years ago, the existing processing methods could not be simply considered as pseudoscience. This is because the irrational preparations and formula must have been eliminated by thousands of years of clinical practices. Although some previous studies have observed heating time- and temperature- dependent effects of some processing methods on HMF contents (**Table 2**), more studies are required to investigate optimal CHM processing method(s) for obtaining a desirable accumulation of HMF. Further research on Maillard reaction and caramelization may be helpful to unravel the mysteries of traditional Chinese medicines and their processing for better treatment effects.

Acknowledgement

This work was financially supported by National Natural Science Foundation of China (81072984) and China–Australia Centre for Health Sciences Research.

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