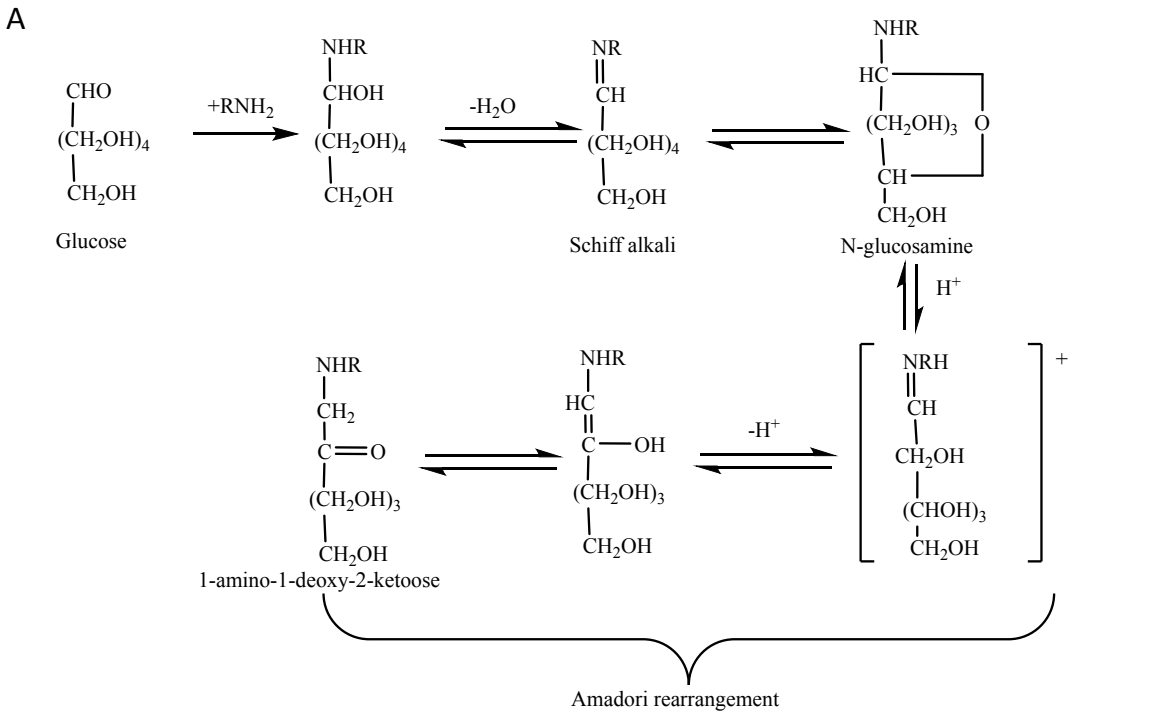
Supplementary Material



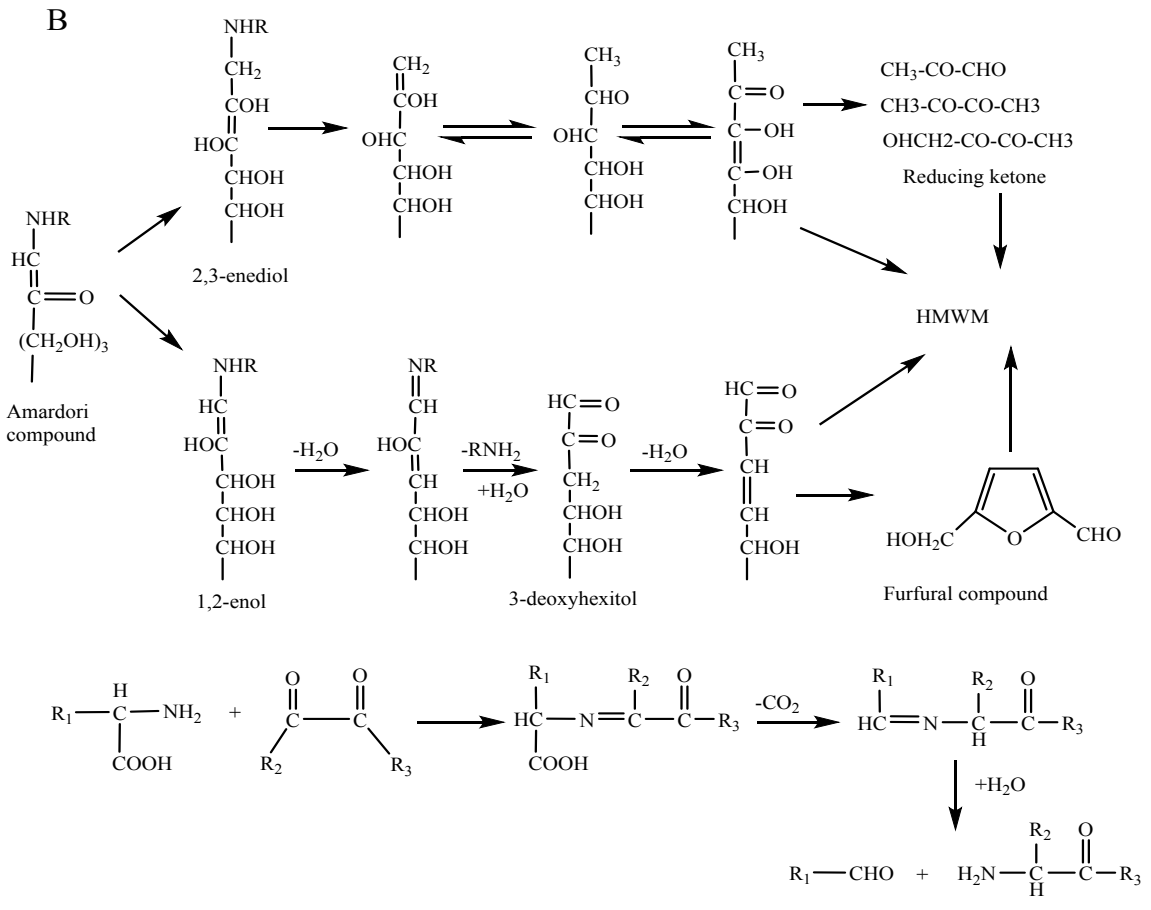


Fig. S. 1 A) The early stage of Maillard reaction. The carbonyl group of the reducing sugar is reacted with an amino group and dehydrated to form a schiff base, which is converted into a reactive 1-amino-1-deoxy-2-ketoose by Amadori rearrangement. B) The middle stage of Maillard reaction, which include three pathways: reducing ketone route, hexose route and Strecker degradation route.

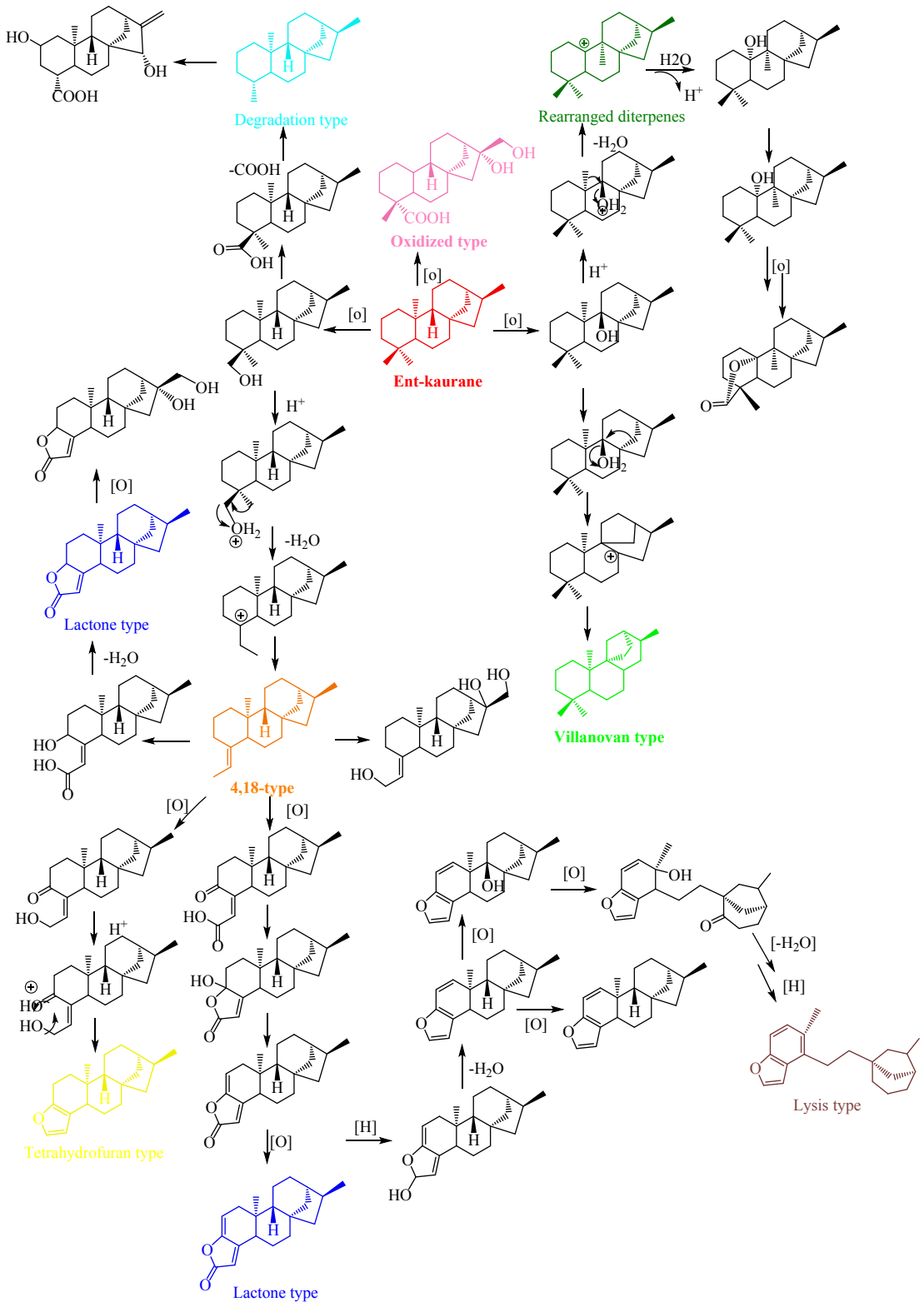


Fig. S. 2 Possible biosynthetic pathways of eight types of diterpenes from coffee. All the coffee diterpenes are derived from the kauran skeleton via oxidation, condensation, rearrangement and other catalytic reactions.

Table S. 1 Studies on the anti-cardiovascular diseases mechanisms of coffee ingredients.

Ingredient	Mechanism	Ref.
CGAs	improve the bioavailability of NO	1,2
CGAs	raise total homocysteine concentrations in plasma	3
polyphenol	enhance energy metabolism; reduces lipogenesis by downregulating SREBP-1c and related molecules.	4
polyphenol	improve postprandial hyperglycemia; vascular endothelial function	5
polyphenol	elevate diastolic blood pressure and and hyperhomocysteinemia	6
polyphenol	enhance energy metabolism; reduces lipogenesis by downregulating SREBP-1c and related molecules.	4
polyphenol	improve postprandial hyperglycemia; vascular endothelial function	5
melanoidins	inhibit angiotensin-I converting enzyme (ACE)	7
C/K	increase the activity of cholesterol transfer proteins	8
caffeine	reduces flow mediated dilation (FMD) in the brachial artery	9
caffeine	improves flow-mediated dilatation	10
Coffee ingredients	reduce the serum levels of triacylglycerols	11
coffee ingredients	raise fasting plasma concentrations of total homocysteine in healthy individuals	12, 13
coffee ingredients	adipocytokines mainly explain the associations of coffee consumption with lipids and high sensitivity C-reactive protein(hs-CRP)	14

Table S. 2 Studies on the antibacterial activities of coffee ingredients.

Compound	Strains	Result	Ref.
3',4'-dihydroxyacetophenone		The antimicrobial activity of the depends on the binding site of the hydroxyl group	15
methylglyoxal; diacetyl and other α-dicarbonyl compounds	*Sa. aureus* and *St. mutans*	Caffeine may synergistically enhance the antibacterial activity of alpha-dicarbonyl compounds	16
Kalata, CirA, CirB, and Cyclopsychotride	Gram-positive and Gram-negative	Kalata and CirA：MIC 0.2 μM. CirB to *E. coli*: MIC 0.41 μM	17
CGA and dodecyl chloride (DCGA)	Gram-positive and Gram-negative	CGA has inhibitory activity against *Pseudomonas fluorescens* and *Staphylococcus aureus;* DCGA is active against Gram-positive bacteria	18
phenolic acids, caffeine, and melanoidins	Gram-positive	These compounds can inhibit Gram-positive bacteria such as *Staphylococcus aureus*, *Listeria monocytogenes*, and yeast (*Candida albicans*)	19
melanoidins	Gram-positive and Gram-negative	Three metal chelate-based antibacterial mechanisms are proposed	20
polysaccharides	*Phoma violacea* and *Cladosporium cladosporioides*	The inhibition rates of these polysaccharides on *Phoma violacea* and *Cladosporium cladosporioides* were 41.27% and 54.60%	21

Table S. 3 Studies on the anti-diabetic mechanisms of coffee ingredients.

Ingredient	Mechanism	Ref.
caffeine	inhibits the misfolding of human amylin polypeptide (hIAPP)	22
caffeine	associates with higher adiponectin and lower inflammatory marker concentrations.	23
CGAs and CA	inhibit AChE activity in diabetic rats	24
CGAs	increase the body's insulin response	25
svetol	inhibits glucose-6-phosphatase hydrolysis in human liver microsomes	26
trigonelline	improves symptoms of diabetes in rats by regulating glucose and lipid metabolism key enzymes	27
trigonelline	improves auditory threshold changes and delay the latency of auditory evoked potentials	28
trigonelline	improves diabetes-induced skeletal system diseases	29

Table S. 4 Studies on the neuroprotection mechanisms of coffee ingredients.

Ingredient	Mechanism	Ref.
caffeine	blocks A2 adenosine receptors	30
caffeine	blocks adenosine A(1) and A(2A) receptors	30
caffeine	reduces both brain and plasma A beta levels	31
caffeine	enhances plasma granulocyte-colony stimulating factor (GCSF) levels	32

coffee ingredients	counteracte Th1-type cytokine interferon-gamma（IFN-gamma-） mediated breakdown of tryptophan	33
cafestol	activates the cytoprotective transcription factor Nrf2	34
eicosanoyl-5-hydroxytryptamide (EHT)	ameliorates the phenotype of alpha-synuclein transgenic mice associated with decreased protein aggregation and phosphorylation, improved neuronal integrity and reduced neuroinflammation	35
eicosanoyl-5-hydroxytryptamide (EHT)	increases the phosphoprotein phosphatase 2A (PP2A) activity by inhibiting the demethylation of its catalytic subunit PP2A	36, 37

Table S. 5 Studies on the anticancer mechanisms of coffee ingredients.

Ingredient	Mechanism	Ref.
HMWM	inhibit the activities of MMP-1, MMP-2 and MMP-9 to prevent colorectal cancer	38
CGAs	induce selective killing of lung cancer cells	41
CGAs	inhibit CT-26 colon cancer cell-induced lung metastasis by blocking the phosphorylation of extracellular regulatory protein kinase (ERK)	39
CGAs	reduce DNA methylation by inhibiting DNA methyltransferases	40
CGAs	induce high levels of topoisomerase I and topoisomerase II-DNA complexes in cells	41
CGAs	inhibit DNA methyltransferase 3a	42
CGAs	stimulate MCF-7 cell growth and that this effect is mediated through ER,	43
kahweol	induces apoptosis through activating transcription factor 3-mediated pathway in human colorectal	44

	cancer cells.	
kahweol	kahweol-mediated cyclin Dl degradation may contribute to the inhibition of the proliferation in human colorectal cancer cells.	45
kahweol	inhibits metastasis through the disruption of STAT3-mediated transcription of themetalloproteinase	46
kahweol	inhibits both COX-2 expression and MCP-1 secretion in endothelial cells	47
kahweol	down-regulation of Bcl-2 and c-FLIP contributes to the sensitizing effect of kahweol on TRAIL-mediated apoptosis in cancer cells	48
C&K	increase overall glutathione transferase (Rakvaag & Dragsted) and GST classes alpha, mu, and enhance UDP-glucuronosyl transferase and GST-theta	49
C&K	Sp1 can be a novel molecular target of cafestol and kahweol in human Malignant pleural mesothelioma	50
C&K	inhibit CYP450s by tendency but not universally	51
C&K palmitates	convert rapid acetylators to a slow acetylator phenotype, accompanied by GST induction, might contribute to chemoprevention against cancers associated with heterocyclic amines	52
C&K; caffeine; CGAs	induce phase II detoxifying and antioxidant enzymes; inhibit the expression or decrease the activity of phase I activating enzymes	53
caffeic acid	people with Fanconi Anemia, or healthy people who develop sporadic mutations in DNA repair protein Fanconi Anemia D2, may be hypersensitive to the carcinogenic activity of coffee.	54
caffeic acid	targets MEK1 and TOPK to suppress colon cancer metastasis and neoplastic cell transformation	39

caffeic acid; CGAs	inhibit in a concentration-dependent manner the DNA methylation catalyzed by prokaryotic M.SssI DNA methyltransferase (DNMT) and human DNMT1.	40
trigonelline	increases the sensitivity of pancreatic cancer and colon cancer cell lines to anticancer drugs by inhibiting Nrf2 activity	55
trigonelline	induces the proliferation of MCF-7 breast cancer cells	43
N-methylpyridinium	reduces menadione-induced DNA damage in Caco-2 cells	56
N-caffeoyltryptophan	may be a potent Sirt1/2 inhibitor with potential use in anticancer	57
coffee ingredients	suppress the effect of the insulin-like growth factor receptor 1 (IGF1R) levels in breast cancer cells	58
coffee ingredients	reduce KRAS activity, thereby preventing the malignant growth of colon carcinoma cells	59
coffee ingredients	inhibit BaP-induced production of oxidative stress by UDP-glucuronosyltransferases activation	60
coffee ingredients	induce HT-29 cell apoptosis to prevent colon cancer	61
coffee ingredients	inhibit adenocarcinoma SW480 growth (LC50-19%) dose dependently by decreasing glutathione/oxidized glutathione (GSH/GSSG) ratio	62
coffee ingredients	activate androgenic AKR1C3 expression mediated by Nrf2 in human prostate cancer cells and therefore may increase the risk of prostate cancer	63
coffee ingredients	inhibit TNF alpha-induced Nuclear Factor-kappa B activity and DNA-binding in prostate cancer cells	64

coffee ingredients	restore the catalase system in the liver, exerting its chemopreventive effects	65
coffee ingredients	the inverse association of coffee intake with cancer-hepatocellular carcinoma risk was partly accounted for by biomarkers of inflammation and hepatocellular injury.	66
coffee ingredients	prevents hepatitis and liver carcinogenesis by reducing the expression of inflammatory cytokines	67
coffee ingredients	decrease systemic oxidative DNA damage through decreasing body iron storage in women.	68
coffee ingredients	may reduce estrogen SULT activity, thereby enhancing estrogenic activity in the colon to prevent colon cancer	69
coffee ingredients	induce breast cancer resistance protein (BCRP) expression in the gastrointestinal tract and may affect the bioavailability of BCRP substrates	70
coffee ingredients	coffee-mediated stimulation of the Nrf2-ARE pathway resulting in increased endogenous defense mechanisms	71
coffee ingredients	cause induction of GSTs and protects against DNA-damage caused by (+/-)-anti-B[a]P-7,8-dihydrodiol-9,10-epoxide (BPDE	72

References

1. R. Ochiai, H. Jokura and T. Ogihara, Green coffee bean extract improves human vasoreactivity, *Hypertens. Res.*, 2004, **27**, 731-737.

2. A. Suzuki, A. Fujii and I. Saito, Improvement of hypertension and vascular dysfunction by hydroxyhydroquinone-free coffee in a genetic model of hypertension, *Febs Lett.*, 2016, **580**,

2317-2322.

3. M. R. Olthof, P. C. Hollman, P. L. Zock, and M. B. Katan, Consumption of high doses of chlorogenic acid, present in coffee, or of black tea increases plasma total homocysteine concentrations in humans, *Am. J. Clin. Nutr.*, 2001, **73**, 532-538.

4. T. Murase, K. Misawa, Y. Minegishi, M. Aoki, H. Ominami, Y. Suzuki and T. Hase, Coffee polyphenols suppress diet-induced body fat accumulation by downregulating SREBP-1c and related molecules in C57BL/6J mice, *Am. J. Physiol.-Endoc. M.,* 2011, **300**, E122-E133.

5. H. Jokura, I. Watanabe, M. Umeda, T. Hase and A. Shimotoyodome, Coffee polyphenol consumption improves postprandial hyperglycemia associated with impaired vascular endothelial function in healthy male adults, *Nutr. Res.*, 2015, **35**, 873-881.

6. A. M. Miranda, J. Steluti, R. M. Fisberg and D. M. Marchioni, Association between coffee consumption and its polyphenols with cardiovascular risk factors: A population-based study, *Nutrients,* 2017, **9**, 276.

7. J. A. Rufian-Henares and F. J. Morales, Effect of in vitro enzymatic digestion on antioxidant activity of coffee melanoidins and fractions, *J. Agr. Food Chem.*, 2009, **57**, 432–438.

8. A. H. M. Terpstra and M. B. Katan, The hypercholesterolemic effect of cafestol in coffee oil in gerbils and rats, *J. Nutri. Biochem.*, 2000, **11**, 311-317.

9. S. Buscemi, A. Mattina, M. R. Tranchina and S. Verga, Acute effects of coffee on QT interval in healthy subjects, *Nutr. J.*, 2011, **10**, 15.

10. E. A. J. Boon, K. D. Croft and N. C. Ward, The acute effect of coffee on endothelial function

and glucose metabolism following a glucose load in healthy human volunteers, *Food & Funct.*, 2017, **8**, 3366-3373.

11. L. F. Brito, L. D. de Queiros, M. D. G. Peluzio, S. M. R. Ribeiro and J. H. Queiroz, Effect of dry coffee residues fermented with monascus ruber on the metabolism of apo E mice, *Arq. Bras. Cardiol.*, 2012, 99, 747-753.

12. M. J. Grubben, G. H. Boers, H. J. Blom and M. B. Katan, Unfiltered coffee increases plasma homocysteine concentrations in healthy volunteers: a randomized trial, *Am. J. Clin. Nutr.*, 2000, **71**, 480-484.

13. R. Urgert, T. van Vlie, P. L. Zock and M. B. Katan, Heavy coffee consumption and plasma homocysteine: a randomized controlled trial in healthy volunteers, *Am. J. Clin. Nutr.*, 2000, **72**, 1107-1110.

14. K. Yamashita, H. Yatsuya, T. Muramatsu and K. Tamakoshi, Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: a cross-sectional study, *Nutr. Diabetes,* 2012, **2**, e33-e33.

15. A. Nishina, F. Kajishima, M. Matsunaga and T. Osawa, Antimicrobial substance, 3',4'-Dihydroxyacetophenone, in coffee residue, *Biosci. Biotech. Biochem.*, 1994*,* **58**, 293-296.

16. M. Daglia, A. Papetti, P. Grisoli, C. Aceti and G. Gazzani, Isolation, identification, and quantification of roasted coffee antibacterial compounds, *J. Agr. Food Chem.*, 2007, **55**, 10208-10213.

17. J. P. Tam, Y. A. Lu, J. L. Yang and K. W. Chiu, An unusual structural motif of antimicrobial

peptides containing end-to-end macrocycle and cystine-knot disulfides, *P. Natl. Acad. Sci. USA*, 1999, **96**, 8913-8918.

18. M. L. Suarez-Quiroz, W. Taillefer, E. M. L. Mendez, O. Gonzalez-Rios and M. C. Figueroa-Espinoza, Antibacterial activity and antifungal and anti-aycotoxigenic activities against *aspergillus alavus* and A. Achraceusof green coffee chlorogenic acids and dodecyl chlorogenates, *J. Food Safety*, 2013*,* **33**, 360-368.

19. C. Monente, J. Bravo, A. I. Vitas, L. Arbillaga, M. P. De Pena and C. Cid, Coffee and spent coffee extracts protect against cell mutagens and inhibit growth of food-borne pathogen microorganisms, *J. Func. Foods*, 2015, **12**, 365-374.

20. J. A. Rufian-Henares and S. P. de la Cueva, Antimicrobial activity of coffee melanoidins-A study of their metal-chelating properties, *J. Agr. Food Chem.*, 2009, **57**, 432-438.

21. L. F. Ballesteros, M. A. Cerqueira, J. A. Teixeira and S. I. Mussatto, Characterization of polysaccharides extracted from spent coffee grounds by alkali pretreatment, *Carbohyd. Polym.*, 2015, **127**, 347-354.

22. B. A. Cheng, X. R. Liu, H. Gong, L. Q. Huang and K. Huan, Coffee components inhibit amyloid formation of human islet amyloid polypeptide in vitro: possible link between coffee consumption and diabetes mellitus, *J. Agr. Food Chem.*, 2011, **59**, 13147-13155.

23. C. J. Williams, J. L. Fargnoli, J. J. Hwang and C. S. Mantzoros, Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes - A prospective cohort study, *Diabetes Care,* 2008, **31**, 504-507.

24. N. Stefanello, R. Schmatz, L. B. Pereira, M. A. Rubin, J. B. T. da Rocha and M. R. C. Schetinger, Effects of chlorogenic acid, caffeine, and coffee on behavioral and biochemical parameters of diabetic rats, *Mol. Cell. Biochem.*, 2014, **388**, 277-286.

25. B. Fernandez-Gomez, A. Lezama, M. Amigo-Benavent and del M. D. Castillo, Insights on the health benefits of the bioactive compounds of coffee silverskin extract, *J. Func. Foods*, 2016, **25**, 197-207.

26. C. Henry-Vitrac, A. Ibarra, M. Roller and X. Vitrac, Contribution of chlorogenic acids to the Inhibition of human hepatic glucose-6-phosphatase activity in vitro by svetol, a standardized decaffeinated green coffee extract, *J. Agr. Food Chem.*, 2010, **58**, 4141-4144.

27. O. Yoshinari, H. Sato, and K. Igarashi, Anti-diabetic effects of pumpkin and its components, trigonelline and nicotinic acid, on Goto-Kakizaki rats, *Biosci. Biotechnol. Biochem.*, 2009, **73**, 1033-1041.

28. B. N. Hong, T. H. Yi, R. Park and T. H. Kang, Coffee improves auditory neuropathy in diabetic mice, *Neurosci. Lett.*, 2008, **441**, 302-306.

29. J. Folwarczna, A. Janas, M. Pytlik and M. Gajdos, Effects of trigonelline, an alkaloid present in coffee, on diabetes-induced disorders in the rat skeletal system, *Nutrients*, 2016, **8**, 133.

30. J. Trevitt, K. Kawa, A. Jalali and C. Larsen, Differential effects of adenosine antagonists in two models of parkinsonian tremor. *Pharmacol. Biochem. Behav.*, 2009, **94**, 24-29.

31. G. W. Arendash and C. H. Cao, Caffeine and coffee as therapeutics against alzheimer's disease, *J. Alzheimers Dis.*, 2010, **20**, S117-S126.

32. C. H. Cao, L. Wang, X. Y. Lin, M. Mamcarz and G. Arendash, Caffeine synergizes with another coffee component to increase plasma GCSF: Linkage to cognitive benefits in alzheimer's mice, *J. Alzheimers Dis.*, 2011, **25**, 323-335.

33. J. M. Gostner, S. Schroecksnadel, M. Jenny, A. Klein and D. Fuchs, Coffee extracts suppress tryptophan breakdown in mitogen-stimulated peripheral blood mononuclear cells, *J. Am. Coll. Nutr.*, 2015, **34**, 212-223.

34. K. Trinh, L. Andrews, J. Krause, T. Hanak and L. Pallanck, Decaffeinated coffee and nicotine-free tobacco provide neuroprotection in drosophila models of parkinson's disease through an NRF2-dependent mechanism, *J. Neurosci.*, 2010, **30**, 5525-5532.

35. K. W. Lee, J. Y. Im, J. M. Woo and M. M. Mouradian, Neuroprotective and anti-inflammatory properties of a coffee component in the MPTP model of parkinson's disease, *Neurotherapeutics*, 2013, **10**, 143-153.

36. G. Basurto-Islas, J. Blanchard, Y. C. Tung and K. Iqbal, Therapeutic benefits of a component of coffee in a rat model of Alzheimer's disease, *Neurobiol. Aging,* 2014, **35**, 2701-2712.

37. K. Asam, A. Staniszewski, H. Zhang and R. E. Nicholls, Eicosanoyl-5-hydroxytryptamide (EHT) prevents Alzheimer's disease-related cognitive and electrophysiological impairments in mice exposed to elevated concentrations of oligomeric beta-amyloid, *Plos One*, 2017, **12**, e0189413.

38. L. M. De Marco, S. Fischer and T. Henle, High molecular weight coffee melanoidins are inhibitors for matrix metalloproteases, *J. Agr. Food Chem.*, 2011, **59**, 11417-11423.

39. N. J. Kang, K. W. Lee, B. H. Kim and Z. Dong, Coffee phenolic phytochemicals suppress colon cancer metastasis by targeting MEK and TOPK, *Carcinogenesis*, 2011, **32**, 921-928.

40. W. J. Lee and B. T. Zhu, Inhibition of DNA methylation by caffeic acid and chlorogenic acid, two common catechol-containing coffee polyphenols, *Carcinogenesis*, 2006, **27**, 269-277.

41. E. Burgos-Moron, J. M. Calderon-Montano, M. L. Orta, N. Pastor and M. Lopez-Lazaro, The coffee constituent chlorogenic acid Induces cellular DNA damage and formation of topoisomerase I- and II-DNA complexes in cells, *J. Agr. Food Chem.*, 2012, **60**, 7384-7391.

42. A. Rajavelu, Z. Tulyasheva, R. Jaiswal and N. Kuhnert, The inhibition of the mammalian DNA methyltransferase 3a (Dnmt3a) by dietary black tea and coffee polyphenols, *Bmc Biochem.*, 2011, **12**, 16.

43. K. F. Allred, K. M. Yackley, J. Vanamala and C. D. Allred, Trigonelline is a novel phytoestrogen in coffee beans, *J. Nutr.*, 2009, **139**, 1833-1838.

44. G. H. Park, H. M. Song and J. B. Jeong, Kahweol from coffee induces apoptosis by upregulating activating transcription factor 3 in human colorectal cancer cells, *Biomol. Ther.*, 2017, **25**, 337-343.

45. G. H. Park, H. M. Song and J. B. Jeong, The coffee diterpene kahweol suppresses the cell proliferation by inducing cyclin D1 proteasomal degradation via ERK1/2, JNK and GKS3 beta-dependent threonine-286 phosphorylation in human colorectal cancer cells, *Food Chem. Toxicol.*, 2016, **95**, 142-148.

46. H. G. Kim, Y. P. Hwang, E. H. Han and H. G. Jeong, The coffee diterpene kahweol inhibits

metastasis by modulating expressions of MMPs and VEGF via STAT3 inactivation, *Food Chem.*, 2012, **133**, 1521-1529.

47. C. Cardenas, A. R. Quesada and M. A. Medina, Anti-Angiogenic and anti-inflammatory properties of kahweol, a coffee diterpene, *Plos One*, 2011, **6**. e23407.

48. H. J. Um, J. H. Oh, Y. N. Kim, Y. H. Choi and T. K. Kwon, The coffee diterpene kahweol sensitizes TRAIL-induced apoptosis in renal carcinoma Caki cells through down-regulation of Bcl-2 and c-FLIP, *Chem.-Biol. Interact.*, 2010, **186**, 36-42.

49. W. W. Huber, S. Prustomersky, E. Delbanco and R. Schulte-Hermann, Enhancement of the chemoprotective enzymes glucuronosyl transferase and glutathione transferase in specific organs of the rat by the coffee components kahweol and cafestol, *Arch. Toxicol.*, 2002, **76**, 209-217.

50. K. A. Lee, J. I. Chae and J. H. Shim, Natural diterpenes from coffee, cafestol and kahweol induce apoptosis through regulation of specificity protein 1 expression in human malignant pleural mesothelioma, *J. Biomed. Sci.*, 2012, **19**, 60.

51. W. W. Huber, W. Rossmanith, M. Grusch and R. Schulte-Hermann, Effects of coffee and its chemopreventive components kahweol and cafestol on cytochrome P450 and sulfotransferase in rat liver, *Food Chem. Toxicol.*, 2008, **46**, 1230-1238.

52. W. W. Huber, C. H. Teitel, B. F. Coles and F. F. Kadlubar, Potential chemoprotective effects of the coffee components kahweol and cafestol palmitates via modification of hepatic N-acetyltransferase and glutathione S-transferase activities, *Environ. Mol. Mutagen.*, 2004, **44**,

265-276.

53. K. S. Tao, W. Wang, L. Wang, D. Y. Cao, Y. Q. Li and K. F. Dou, The multifaceted mechanisms for coffee's anti-tumorigenic effect on liver, *Med. Hypotheses*, 2008, **71**, 730-736.

54. E. Burgos-Moron, J. M. Calderon-Montano, M. L. Orta, E. Guillen-Mancina and M. Lopez-Lazaro, Cells deficient in the fanconi anemia protein FANCD2 are hypersensitive to the cytotoxicity and DNA damage induced by coffee and caffeic acid, *Toxins*, 2016, **8**, 211.

55. A. Arlt, S. Sebens, S. Krebs, C. Geismann and H. Schafer, Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity, *Oncogene*, 2013, **32**, 4825-4835.

56. T. Bakuradze, R. Lang, T. Hofmann, H. Stiebitz and C. Janzowski, Antioxidant effectiveness of coffee extracts and selected constituents in cell-free systems and human colon cell lines, *Mol. Nutr. Food Res.*, 2010, **54**, 1734-1743.

57. J. B. Park, Finding potent sirt inhibitor in coffee: Isolation, confirmation and synthesis of javamide-II (N-Caffeoyltryptophan) as sirt1/2 inhibitor, *Plos One*, 2016, **11**, e0150392.

58. S. Bjorner, A. H. Rosendahl, H. Tryggvadottir, M. Simonsson and H. Jernstrom, Coffee is associated with lower breast tumor insulin-like growth factor receptor 1 levels in normal-weight patients and improved prognosis following tamoxifen or radiotherapy treatment, *Front. Endocrinol.*, 2018, **9**.

59. T. Nakayama, M. Funakoshi-Tago and H. Tamura, Coffee reduces KRAS expression in Caco-2 human colon carcinoma cells via regulation of miRNAs, *Oncol. Lett.*, 2017, **14**, 1109-1114.

60. S. Kalthoff, S. Landerer, J. Reich and C. P. Strassburg, Protective effects of coffee against oxidative stress induced by the tobacco carcinogen benzo[alpha]pyrene, *Free Radical Bio. Med.*, 2017, **108**, 66-76.

61. A. M. Hernandez-Arriaga, B. D. Oomah and R. Campos-Vega, Microbiota source impact in vitro metabolite colonic production and anti-proliferative effect of spent coffee grounds on human colon cancer cells (HT-29), *Food Res. Int.*, 2017, **97**, 191-198.

62. N. Garcia-Gutierrez, M. E. Maldonado-Celis, M. Rojas-Lopez, G. F. Loarca-Pina and R. Campos-Vega, The fermented non-digestible fraction of spent coffee grounds induces apoptosis in human colon cancer cells (SW480), *J. Func. Foods*, 2017, **30**, 237-246.

63. K. Takahashi, M. Funakoshi-Tago, M. Takaoka, S. Kakio and H. Tamura, Roasted coffee induction of aldo-keto reductase 1C3 expression in LNCaP human prostate cancer cells is associated with Nrf2 activation, *Oncol. Let.*, 2016, **12**, 5321-5326.

64. M. Kolberg, S. Pedersen, M. Mitake, K. L. Holm and I. Paur, Coffee inhibits nuclear factor-kappa B in prostate cancer cells and xenografts, *J. Nutr. Biochem.*, 2016, **27**, 153-163.

65. C. S. de Magalhaes, J. E. Takarada, N. C. Carvalho, D. D. Carvalho, F. L. de Andrade, E. B. Ferreira, P. O. Luccas and L. Azevedo, The coffee protective effect on catalase system in the preneoplastic induced rat liver, *J. Chem.*, 2016, 1-9.

66. K. Aleksandrova, C. Bamia, D. Drogan and P. Lagiou, The association of coffee intake with

liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition, *Am. J. Clin. Nutr.*, 2015, **102**, 1498-1508.

67. M. Katayama, K. Donai, H. Sakakibara, Y. Ohtomo and T. Fukuda, Coffee consumption delays the hepatitis and suppresses the inflammation related gene expression in the Long-Evans Cinnamon rat, *Clin. Nutr.*, 2014, **33**, 302-310.

68. A. Hori, H. Kasai, K. Kawai and T. Mizoue, Coffee intake is associated with lower levels of oxidative DNA damage and decreasing body iron storage in healthy women, *Nutr. Cancer*, 2014, **66**, 964-969.

69. M. Isshiki, H. Ohta and H. Tamura, Coffee reduces SULT1E1 expression in human colon carcinoma Caco-2 Cells, *Biol. Pharm. Bull.*, 2013, **36**, 299-304.

70. M. Isshiki, K. Umezawa and H. Tamura, Coffee induces breast cancer resistance protein expression in Caco-2 cells, *Biol. Pharm. Bull.*, 2011, **34**, 1624-1627.

71. C. Cavin, M. Marin-Kuan, S. Langouet, C. Bezencon and B. Schilter, Induction of Nrf2-mediated cellular defenses and alteration of phase I activities as mechanisms of chemoprotective effects of coffee in the liver, *Food Chem. Toxicol.*, 2008, **46**, 1239-1248.

72. H. Steinkellner, C. Hoelzl, M. Uhl, C. Cavin and S. Knasmuller, Coffee consumption induces GSTP in plasma and protects lymphocytes against (+/-)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide induced DNA-damage: Results of controlled human intervention trials, *Mutat. Res.-Fund. Mol. M.*, 2005, **591**, 264-275.