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MINI REVIEW

Carcinogenicity of dietary MeIQx in the prostate, breast, colon, and liver cancers, and the inhibitory effects of some compounds on MeIQx: a mini review

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Abstract

Heterocyclic amines (HCAs) are among the most common toxic compounds formed in food, particularly protein-rich foods when prepared at high temperatures for an extended period. To date, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) is considered one of the most abundant HCAs. However, only a few studies have been conducted on MeIQx, particularly on its carcinogenic potential, despite being labelled as Group 2B Carcinogens by the International Agency for Research on Cancer. MeIQx has been shown to contribute to various types of cancer such as prostate, breast, colon and liver cancers. In most cancers, the genotoxic metabolites of MeIQx induce cancer primarily through the formation of DNA-carcinogen adducts, although some studies show their association with oxidative damage. Nonetheless, the involvement of various enzymes such as N-acetyltransferase, sulfotransferases, and glutathione S-transferases equally plays a crucial role in determining whether this carcinogen undergoes bio-activation or detoxification. This review sought to highlight the most recent research on the carcinogenic effects of MeIQx in prostate, colon, breast, and liver cancers, and provide a list of some potential compounds that can inhibit MeIQx formation. Epidemiological studies exploring the association between MeIQx exposure and prostate, breast and colon cancers produced mixed results. However, most of the experimental studies demonstrated the carcinogenic role of MeIQX in prostate, breast, colon, and liver cancers in both *in vitro* and *in vivo* models. Further investigation on the effects of its consumption on human health is needed which may help in understanding and reducing its potential to cause cancer. The inhibitory properties of other natural compounds on this carcinogen should also be explored.

1. Introduction

Cancer has long been regarded as a public health problem that affects people of all ages and places a significant psychological, financial, and social burden on those affected. Smoking, poor dietary habits, and obesity are among the major factors found to be strongly associated with the incidence of most cancers (Fitzmaurice *et al*., 2015). In terms of dietary intake, carcinogenic food-borne heterocyclic amines (HCAs) have piqued the interest of researchers all over the world, and this group of compounds has been extensively studied over the last 20 years to elucidate their possible mode of actions or mechanisms to mitigate their carcinogenic effects. Along with polycyclic aromatic hydrocarbons (PAH) and nitroso-compounds (NOH), HCAs are some of the most common types of carcinogens formed during the high-temperature cooking of proteinaceous foods. HCAs can be classified into two main groups based on the temperature at which they form: thermic (100 - 300°C) and pyrolytic (above 300° C) HCAs (Kang *et al*., 2022). HCAs' formation is also heavily influenced by aspects such as cooking time, cooking method, cooking temperature, and concentration of precursors (Li *et al*., 2020). HCAs were first identified in 1977 when Professor Sugimura discovered the presence of carcinogenic compounds in meat during cooking and subsequently named them HCAs (Khan *et al*., 2022). To the best of our knowledge, 33 HCAs have been identified to date as shown in Table 1, and some of these HCAs have been classified by the International Agency for Research on Cancer (IARC) as probable carcinogens (Group 2A) and possible human carcinogens (Group 2B) (Alaejos and Afonso, 2011).

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Table 1. List of heterocyclic amines and their classification according to the International Agency for Research on Cancer (IARC)

Number	Heterocyclic aromatic amine (HCA)	Abbreviated name	IARC Class
Thermic HCAs			
1	2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine	PhIP	Group 2B
2	2-amino-1-methyl-6-(4'-hydroxyphenyl)imidazo[4,5-*b*]pyridine	4'-OH-PhIP	-
3	2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine	DMIP	-
4	2-amino-1,5,6-trimethylimidazo[4,5-*b*]pyridine	1,5,6-TMIP	-
5	2-amino-3,5,6-trimethylimidazo[4,5-*b*]pyridine	3,5,6-TMIP	-
6	2-amino-1,6-dimethyl-furo[3,2-*e*]imidazo[4,5-*b*]pyridine	IFP	-
7	2-amino-1-methylimidazo[4,5-*f*]quinoline	iso-IQ	-
8	2-amino-3-methylimidazo[4,5-*f*]quinoline	IQ	Group 2A
9	2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline	MeIQ	Group 2B
10	2-amino-1-methylimidazo[4,5-*b*]quinoline	IQ[4,5-*b*]	-
11	2-amino-3-methylimidazo[4,5-*f*]quinoxaline	IQx	-
12	2-amino-3,4-dimethylimidazo[4,5-*f*]quinoxaline	4-MeIQx	-
13	2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline	MeIQx	Group 2B
14	2-amino-3,7,8-trimethylimidazo[4,5-*f*]quinoxaline	7,8-DiMeIQx	-
15	2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline	4,8-DiMeIQx	-
16	2-amino-4-hydroxymethyl-3,8-dimethylimidazo[4,5-*f*]quinoxaline	4-CH_2OH-8-MeIQx	-
17	2-amino-3,4,7,8-tetramethylimidazo[4,5-*f*]quinoxaline	TriMeIQx	-
18	2-amino-1-methylimidazo[4,5-*g*]quinoxaline	IgQx	-
19	2-amino-1,7-dimethylimidazo[4,5-*g*]quinoxaline	7-MeIgQx	-
20	2-amino-1,6,7-trimethylimidazo[4,5-*g*]quinoxaline	6,7-DiMeIgQx	-
21	2-amino-1,7,9-trimethylimidazo[4,5-*g*]quinoxaline	7,9-DiMeIgQx	-
Pyrolitic HCAs			
22	2-aminodipyrido[1,2-*a*:3',2'-*d*]imidazole	Glu-P-2	Group 2B
23	2-amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole	Glu-P-1	Group 2B
24	3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole	Trp-P-2	Group 2B
25	3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole	Trp-P-1	Group 2B
26	1-methyl-9*H*-pyrido[3,4-*b*]indole	Harman	-
27	9*H*-pyrido[3,4-*b*]indole	Norharman	-
28	2-amino-5-phenylpyridine	Phe-P-1	-
29	2-amino-9*H*-pyrido[2,3-*b*]indole	AαC	Group 2B
30	2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole	MeAαC	Group 2B
31	4-amino-6-methyl-1*H*-2,5,10,10*b*- tetraazafluoranthene	Orn-P-1	-
32	4-amino-1,6-dimethyl-2-methylamino- 1*H*,6*H*-pyrrolo-[3,4-*f*]benzimidazole -5,7-dione	Cre-P-1	-
33	3,4-cyclopenteno-pyrido[3,2-*a*]carbazole	Lys-P-1	-

Source: Alaejos and Afonso (2011).

One of the most abundant HCAs that has been reported in most of the studies carried out on HCAs and is a Group 2B by IARC is 2-amino-3,8-dimethylimidazo [4,5-*f*]quinoxaline (MeIQx) (Li *et al*., 2021). However, the evidence supporting MeIQx's carcinogenic consequences is scarce. Therefore, this article aimed to review the carcinogenic effects of dietary MeIQx on prostate, colon, breast, and liver cancers. Some compounds which exhibited inhibitory effects on MeIQx formation are also included.

2. MeIQx

MeIQx was first isolated and identified by Kasai *et al*. (1981). This compound has been shown to form in chicken, beef, fish, and mutton which are cooked under high temperatures ranging from 200°C to 210°C for a long period (Khan *et al*., 2009; Zaidi *et al*., 2012). MeIQx content in grilled patties from various animal species ranges from 0.49 to 1.35 ng/g (Nadeem *et al*., 2021). Among the HCAs classified as possibly carcinogenic by IARC, the MeIQx formation pathway is still largely unknown (Hidalgo *et al*., 2021). MeIQx can either be bioactivated or undergo detoxification depending on this compound's concentration and the involvement of various enzymes such as CYP1A2 and UGT (Delannée *et al*., 2017). Figure 1 shows the enzymes involved and the resulting metabolites in the well-established metabolism of MeIQx (Delannée *et al*., 2017). As shown in Figure 1, MeIQx has to be first metabolically activated by cytochrome P450 to exert its genotoxicity and carcinogenicity. Once metabolically

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activated, MeIQx goes through a series of events, including N-hydroxylation and esterification, and eventually forms the MeIQx-DNA adducts. Previously, Hartwig *et al*. (2020) identified *N*-(deoxyguanosin-8-yl)-MeIQx (dG-C8-MeIQx) as the major adduct and 5-(deoxyguanosin-N^2-yl)-MeIQx (dG-N^2-MeIQx) as the minor adduct. Interestingly, this does not apply to *in vivo* studies, particularly studies using a low dose of MeIQx in rats, signifying the different capacities for the biotransformation of this compound in different experimental models. Furthermore, dG-N^2-MeIQx also appears to contribute significantly to the genotoxic damage caused by MeIQx (Hartwig *et al*., 2020). Nauwelaërs *et al.* (2013) have established the nucleotide excision repair (NER) complex mechanism as a prominent means of eliminating adducts caused by heterocyclic amines. At the initial stage, the dG-C8 adducts of MeIQx formed can be removed by either global genome repair (GG-NER) or transcription-coupled repair (TC-NER). Their findings also showed that a significant proportion of the dG-C8-MeIQx adducts in genomic DNA persist in human hepatocytes.

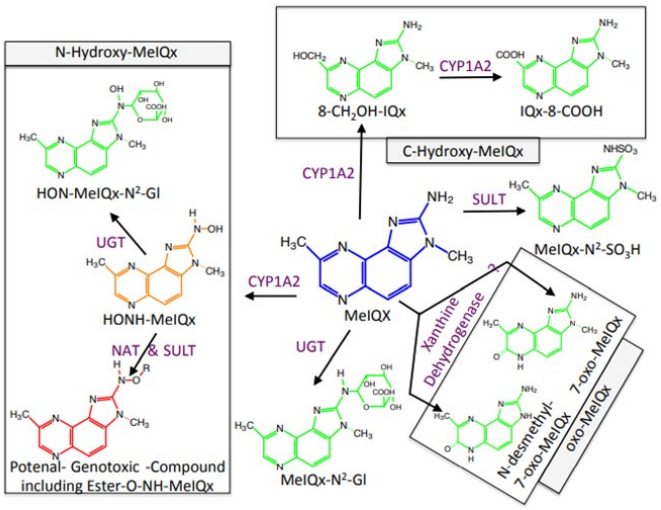

Figure 1. Metabolic pathways of MeIQx. The detoxification pathway and bioactivation pathway of MeIQx are emphasized in green and red/orange respectively. Full chemical names: MeIQx: 2-amino-3:8- dimethylimidazo[4:5-*f*]quinoxaline, HONH-MeIQx: 2-(hydroxyamino)-3:8-dimethylimidazo[4:5-*f*]quinoxaline, MeIQx-N^2-SO3H: N^2-(3:8-dimethylimidazo[4:5-*f*]quinoxalin-2-yl)sulfamic acid, MeIQx-N^2-Gl: N^2-(β-1-glucosiduronyl)-2-amino-3:8-dimethylimidazo-[4:5-*f*] quinoxaline, 8-CH2OHIQx: 2-amino-8-(hydroxymethyl)-3-meth-ylimidazo[4:5-*f*]quinoxaline, IQx-8-COOH: 2-amino-3-methyl-imidazo[4:5-*f*]quinoxaline-8-carboxylic acid, HON-MeIQx-N^2-Gl: N^2-(β-1-glucosiduronyl)-2-(hydroxyamino)-3:8-dimethylimidazo[4:*f*-f]quinoxaline, 7-oxo-MeIQx: 2-amino-3:8-dimethyl-6-hydro-7*H*-imidazo[4:5-*f*]quinoxalin-7-one, *N*-desmethyl-7-oxo-MeIQx: 2-amino-6-hydro-8-methyl-7*H*-imidazo[4:5-*f*]quinoxalin-7-one
Source: Delannée *et al.* (2017).

2.1 Epidemiological studies

The association between MeIQx exposure and prostate, breast, colon, and liver cancers has been explored in several epidemiological studies which yielded mixed results. The relationship between MeIQx with prostate cancer risk has been investigated and published in several epidemiological studies. Two cohort studies did not show a clear association between MeIQx exposure with prostate cancer risk (Sander *et al*., 2011; Rohrmann *et al*., 2015). On the contrary, MeIQx exposure was found to be associated with an elevated prostate cancer risk in a cohort study conducted in Iowa and North Carolina (Koutros *et al*., 2008) and in a case-control study in Cleaveland, Ohio (Punnen *et al*., 2011), suggesting further research is warranted in examining the association of MeIQx exposure with prostate cancer risk. In addition, a case-control study conducted by Van Hemelrijck *et al*. (2012) with 204 cases and 360 controls in Heidelberg suggested that the association between HCAs intake, including MeIQx, and prostate cancer risk may be modified by genetic polymorphisms in GSTM1 and GSTT1 genes that encode metabolizing enzymes for HCA activation or detoxification. Interestingly, this study found inverse associations between MeIQx intake and prostate cancer risk in patients having less than 2 deletions of GSTM1 and GSTT1 genes.

There have been eight published epidemiological studies that examined the relationship between MeIQx exposure with the risk of breast cancer, comprising four case-control studies (de Stefani *et al*., 1997; Delfino *et al*., 2000; Sinha *et al*., 2000; Steck *et al*., 2007) and four prospective studies (Sonestedt *et al*., 2008; Ferrucci *et al*., 2009; Kabat *et al*., 2009; Wu *et al*., 2010). These studies carried out a detailed assessment of MeIQx exposure and breast cancer risk using the food frequency questionnaire. A case-control study conducted by de Stefani *et al*. (1997) in Uruguay, which comprised 352 cases and 382 controls, showed a positive association between postmenopausal breast cancer risk and MeIQx exposure because of a high intake of fried meats. Their result also showed significant dose-response relationships between breast cancer risk and dietary exposure to MeIQx. In addition, Ferrucci *et al*. (2009) have also demonstrated a positive association between MeIQx exposure and breast cancer risk even though the association is weaker than the aforementioned study. However, in three other case-control studies (Delfino *et al*., 2000; Sinha *et al*., 2000; Steck *et al*., 2007) and three prospective studies (Sonestedt *et al*., 2008; Kabat *et al*., 2009; Wu *et al*., 2010), no association was found between MeIQx exposure and the risk of breast cancer. Additionally, Steck *et al*. (2007) reported that MeIQx intake across quintiles demonstrated a 40% reduction in

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the risk of postmenopausal breast cancer risk and was not linked with premenopausal breast cancer risk.

To date, only two population-based case-control studies have evaluated the potential role of HCAs exposure, including MeIQx, in the aetiology of colon cancer. The first study by Augustsson *et al*. (1999) in Sweden involved 352 cases of colon cancer and 553 controls, and it reported an inverse association between colon cancer risk and the intake of MeIQx. They suggested that meat and fish may contain other carcinogenic compounds such as PAH, nitrosamines, and less polar HCAs that could potentially lead to human carcinogenesis. On the other hand, Nowell *et al.* (2002) conducted a case-control study comprising 157 cases and 380 controls that have been standardized in terms of sex, ethnicity, decade of age, and county of residence. They assessed the relationship between environmental exposure, metabolic polymorphisms, and the risk of colorectal cancer. High intakes of MeIQx were found to be associated with a significant and elevated risk of colorectal cancer due to the role of several enzymes including CYP2A6, hGSTA1, and SULT. It is worth mentioning that all three enzymes play a crucial role in understanding the complex molecular epidemiology of colorectal cancer. SULT's low activity and high expression levels of hGSTA1 were found to contribute to the decreased risk of colorectal cancer, whereas a high CYP2A6 expression level was associated with increased colorectal cancer risk (Nowell *et al*., 2002).

2.2 Carcinogenicity of MeIQx

The list of experimental studies investigating the carcinogenic effects of MeIQx in prostate, breast, colon, and liver cancers as well as their experimental details is summarized in Table 2.

2.3 Prostate cancer

There were no recent studies that investigated MeIQx's carcinogenic mechanisms of action in prostate cancer experimental studies. Going back to almost two decades ago, there was a study conducted by Lawson and Kolar (2002) investigating the potential of human prostate epithelial cells from disease-free donors of two different age groups; 17- and 42-years donors ($HuPrEC_{17}$ and $HuPrEC_{42}$) to metabolize heterocyclic amines and generate genotoxic species. Although cells from different age groups could metabolize MeIQx, the cells from the older donor metabolized comparatively better due to the fast acetylation status of NAT1. In addition, Wang *et al*. (1999) reported that the N-hydroxy metabolite of MeIQx induced MeIQx-DNA adduct formation in human prostate epithelial cells. Archer *et al*. (2000) found that the same metabolite could lead to prostate hyperplasia in rats.

2.4 Breast cancer

A few experimental studies have been conducted to investigate the effects of MeIQx on breast cancer. A study conducted by Gorlewska-Roberts *et al*. (2004) showed that PhIP had the least lactoperoxidase-catalysed activation as well as the lowest binding affinity to DNA compared to other HCAs including MeIQx. The results of the study were further supported by Sheikh *et al*. (2017), who demonstrated that lactoperoxidase (LPO), an antimicrobial protein usually secreted from mammary, saliva, and other mucosal glands could potentially activate MeIQx through oxidation via the interaction of heme ring in LPO with MeIQx. The findings of the study also suggested that the activated MeIQx as an outcome of oxidation by LPO especially in breast tissues may form DNA adducts, which may result in breast carcinogenesis. Interestingly, Bennion *et al*. (2005) found that, unlike PhIP, MeIQx did not stimulate oestrogen receptor alpha (ERα) activity, which plays a major role in stimulating breast cancer cell proliferation. Furthermore, the study also demonstrated that both 1:1 and 1:3 PhIP/MeIQx mixtures inhibit the PhIP from activating ERα activity, suggesting the role of MeIQx as an inhibitory HCA in breast carcinogenesis.

2.5 Colon cancer

Little research has been done on the effect of MeIQx on colon carcinogenesis. In studies conducted by Garner *et al*. (1999) and Turteltaub *et al*. (1999), MeIQx was found to induce DNA adduct formation in rats and humans. Tanakamaru *et al*. (2001) investigated the differences between naturally occurring colon APC and MeIQx-induced colon APC in F344 rats and found that there were no significant differences found in terms of morphology, cell proliferation, p53 expression, and c-K-ras mutation. In another study by Fujita *et al*. (2002), the MeIQx-induced colon aberrant crypt foci (APC) in rats were inhibited by bovine lactoferrin (bLF), an iron-binding glycoprotein usually present in mammalian secretions. In addition, bLF downregulated the levels of CYP1A2 mRNA expression to normal levels, subsequently decreasing the metabolic activation and MeIQx-DNA adduct formation.

2.6 Liver cancer

Several *in vitro* and *in vivo* studies have been conducted to investigate the effect of MeIQx on liver carcinogenesis. Like other cancers discussed above, most of these studies were conducted more than a decade ago. Hirose *et al*. (2000) demonstrated that arctiin, lignan derived from Arctium lappa (burdock) seeds, acts as a weak co-carcinogen as it further increased the number

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Table 2. Studies on carcinogenic effects of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) on prostate, breast, colon, and liver cancers.

Cancer	Study type	Subjects of study	Doses of MeIQx used	Treatment	Effects/potential mechanisms	References
Prostate cancer	*In vitro*	HCV-29 cells (positive controls) and prostate cells	Ranged from 10^{-6}-10^{-4} M	Cells were treated with N-OH-MeIQx	Induce DNA adduct formation and unscheduled DNA synthesis via NATs expression	Wang *et al*. (1999)
	In vivo	ACI/seg rats	50 µmol/kg	Rats were injected with N-OH-MeIQx intraperitoneally twice a week for 10 weeks	Induce atypical hyperplasia of ventral prostate, anterior prostate, and seminal vesicle via metabolic activation of N-OH -MeIQx	Archer *et al*. (2000)
	In vitro	$HuPrEC_{17}$ and $HuPrEC_{42}$	-	Cells were co-cultured with V-79 cells for 16 hours	Modulate the expression of NATs, CYP1A2, and GST, which metabolized the compound to genotoxic species	Lawson and Kolar (2002)
Breast cancer	*In vitro*	LPO	-	MeIQx interacted with LPO in the presence of H_2O_2 and calf thymus DNA	Activate MeIQx in the presence of hydrogen peroxide by producing reactive intermediates to bind with DNA	Gorlewska-Roberts *et al*. (2004)
	Molecular docking (Flexible docking) and *In vitro*	ERα protein; MCF-7 cells	-; 10^{-9}-10^{-5} M	Cells were treated with MeIQx for 48 and 72 hours	Inhibit the activation of ERα	Bennion *et al*. (2005)
	In silico molecular docking	LPO	-	MeIQx interacted with the heme ring of LPO	MeIQx act as an LPO substrate	Sheikh *et al*. (2017)
Colon cancer	*In vivo*	Rats and humans	0.3-3 µg/kg body weight [^{14}C MeIQx]	Rats were given MeIQx by gavage and killed 3.5-6 hours post-dose; Patients were given MeIQx in a gelatine capsule and colon tissue and blood were collected 4.5 hours post-dose	Stimulate MeIQx-DNA adduct formation	Turteltaub *et al*. (1999)
	In vivo	Rats (F344 rats) & humans	182 ng/kg [^{14}C MeIQx]; 20/50/200 µg [^{14}C MeIQx]	Rats were given MeIQx by gavage and killed 48 hours post-dose; Patients were given MeIQx 4-6 hours before surgery for normal and tumour tissue collection	Stimulate MeIQx-DNA adduct formation	Garner *et al*. (1999)
	In vivo	F344 rats	100 ppm	Rats were treated with MeIQx for 16 weeks	No significant differences between spontaneous and MeIQx- promoted aberrant crypt foci in terms of morphology, cell proliferation, p53 expression and K-ras mutation	Tanakamaru *et al*. (2001)

DEN: Diethylnitrosamine, DNA: deoxyribonucleic acids, Erα: oestrogen receptor alpha, FBZ: Fenbendazole, GST: Glutathione S-transferases, H_2O_2: Hydrogen peroxide, HCV-29: Cellosaurus cell line HCV-29, HuPrEC: Human prostate epithelial cells, K-ras: RAS/MAPK pathway protein, LPO: Lactoperoxidase, NATs: N-acetyltransferases, N-OH-MeIQx: N-hydroxy metabolite of MeIQx, p53: Tumour protein.

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Table 2 (Cont.). Studies on carcinogenic effects of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) on prostate, breast, colon, and liver cancers.

Cancer	Study type	Subjects of study	Doses of MeIQx used	Treatment	Effects/potential mechanisms	References
Liver cancer	*In vivo*	CDF_1 mice	0.06% (w/w)	Rats were given a diet containing MeIQx for 84 weeks	Induce liver tumours where females were more susceptible than males	Ohgaki *et al.* (1987)
	In vivo	F344 rats	0.04 (w/w)	Rats were given a diet containing MeIQx for 429 days	Induce carcinoma incidence	Kato *et al.* (1988)
	In vivo	F344 rats	100, 200 and 400 ppm	MeIQx was included in the diet and fed to the rats throughout the experiment	Induce carcinoma incidence in a non-linear manner with the doses employed	Kushida *et al.* (1994)
	In vivo	F344 rats	300 ppm	Rats were treated with DEN as an initiation step and MeIQx alone or with FBZ (600 or 200 ppm) were	FBZ increases CYP1A2 expression, however, the concentration of 600 ppm was insufficient to promote MeIQx-	Suzuki *et al.* (2002)

DEN: Diethylnitrosamine, DNA: deoxyribonucleic acids, Erα: oestrogen receptor alpha, FBZ: Fenbendazole, GST: Glutathione S-transferases, H_2O_2: Hydrogen peroxide, HCV-29: Cellosaurus cell line HCV-29, HuPrEC: Human prostate epithelial cells, K-ras: RAS/MAPK pathway protein, LPO: Lactoperoxidase, NATs: N-acetyltransferases, N-OH-MeIQx: N-hydroxy metabolite of MeIQx, p53: Tumour protein.

and area of preneoplastic GST-P positive foci in MeIQx-induced hepatocarcinogenesis, indicating that arctiin may stimulate the metabolic activation of MeIQx by CYP1A2 in the liver. It is of note that the expression levels of CYP1A2 mRNA were also found to be increased significantly in the livers after MeIQx treatment as reported by Fujita *et al*. (2002) and Takeuchi *et al*. (2010). Suzuki *et al*. (2002) investigated the combined effects of MeIQx with fenbendazole (FBZ), an anthelmintic drug, and found that 2.3-fold higher CYP1A2 expression was observed in the livers of rats given MeIQx and FBZ than MeIQx alone, suggesting the role of FBZ as a CYP1A2 inducer. Kushida *et al*. (1994) demonstrated dose-dependent induction of tumours including liver tumours in F344 rats upon three different MeIQx doses namely 100, 200, and 400 ppm. These findings were in agreement with Kato *et al*. (1988) who found that MeIQx induced liver tumours along with the Zymbal gland, clitoral gland, and skin tumours. In addition, the liver tumour was also induced in mice given a diet containing MeIQx for 84 weeks (Ohgaki *et al*., 1987). Ryu *et al*. (1999) proposed that the synergism between MeIQx and c-myc overexpression contributes to liver carcinogenesis. Furthermore, the study also demonstrated irrespective of the strain of mice, MeIQx-DNA adduct levels were 2-fold greater in females than that in males, suggesting a higher capacity for metabolic activation of MeIQx in the females. This hypothesis is supported by evidence from Ohgaki *et al*. (1987) and Shapiro *et al*. (1995).

3. Inhibitory effects of some compounds on MeIQx

As part of cancer prevention, one of the methods which can be used to reduce the exposure of MeIQx in the diet is by inhibiting its formation in the first place. In a study by Bao *et al*. (2020) who utilized the MeIQx-producing chemical model system, the formation of MeIQx was demonstrated to be inhibited by the pyridoxamine, which was thought to occur as a result of the trapping of the MeIQx intermediate methylglyoxal (MGO). A similar MGO inhibitory mechanism against MeIQx formation was reported by Li *et al*. (2022) using thiamine, a water-soluble vitamin as the subject of interest. Shao *et al*. (2018) demonstrated that several flavonoids such as proanthocyanidin, baicalein, (+)-catechin hydrate, liquiritin, isorhamnetin, isoliquiritin, hesperidin, puerarin, and quercetin inhibited MeIQx formation via alkoxy radical scavenging. Table 3 shows some compounds which were able to inhibit the formation of MeIQx in various samples/model systems.

4. Conclusion

Although epidemiological studies exploring the association between MeIQx exposure and prostate, breast and colon cancers have all yielded mixed results, most of the experimental studies demonstrated the carcinogenicity of MeIQX in prostate, breast, colon, and liver cancers in both *in vitro* and *in vivo* models. The major mechanism of action of MeIQx in all these cancers is through DNA adduct formation which eventually gives rise to tumours/cancers as demonstrated in some of the *in vivo* studies. Although the experimental research exploring the role or mechanisms in which the MeIQx contribute to cancer formation has waned over the years, the risk posed by this compound to people remains high because of its propensity to cause cancer. This is evident as global meat consumption by developing as well as developed nations showed a tremendous increase over the last 20 years, signifying increased risks of associated diseases including cancers (OECD/FAO, 2022). Understanding the association between the consumption of proteinaceous foods rich in heterocyclic amines, such as MeIQx, and the risk of cancers helps in preventing and lowering the latter. As experimental research in elucidating the role of MeIQx and its mechanisms in cancer induction is still insufficient, thorough research is required to comprehend the effect of its consumption on human health, which may aid in lowering its potential to cause cancer. This can be done by, for example, targeting the possible routes leading to their bio-activation and

Table 3. Compounds that inhibit the formation of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx).

No	Compound	Sample/experimental system	References
1	Clove	Beef meat sample	Abou-Baker *et al*. (2015)
2	Apple peel polyphenol extract	Beef patties	Sabally *et al*. (2016)
3	Flavonoids (proanthocyanidin, baicalein, (+) -catechin hydrate, liquiritin, isorhamnetin, isoliquiritin, hesperidin, puerarin and quercetin)	MeIQx-producing model system	Shao *et al*. (2018)
4	Chitosan and flavonoid glycosides	MeIQx-producing chemical model system and roast beef patties	Zhang *et al*. (2020)
5	Pyridoxamine	MeIQx-producing model system	Bao *et al*. (2020)
6	Chlorogenic acid	Charcoal roasted lamb patties	Ding *et al*. (2022)
7	Epicatechin	Charcoal roasted lamb patties	
8	Thiamine	MeIQx-producing model system	Li *et al*. (2022)

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carcinogenic potential.

Considering MeIQx's considerable carcinogenic consequences, researchers have recently started investigating the inhibitory effects of a variety of compounds on MeIQx formation. Some of the compounds which were able to inhibit MeIQx formation are included here. Further research exploring the inhibitory effects of other natural compounds, such as those used in meat marination, against MeIQx formation is needed to lessen the carcinogenic impact of MeIQx. The results of these investigations will also be advantageous to society since these compounds can be used in food preparation and diet. In addition, further research on natural compounds which can reduce the carcinogenic effects or block the mechanism of action of MeIQx in both *in vitro* and *in vivo* models should also be explored.

Conflict of interest

The authors declare no conflict of interest.

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