Elucidation of dibenzo[a,l]pyrene and its metabolites as a mammary carcinogen: A comprehensive review

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**ABSTRACT**

The general mechanism of cancer includes the metabolism of carcinogens to highly electrophilic metabolites capable of binding to DNA and other macromolecules, thereby initiating the cells. As the carcinogenesis mechanism is quite complex where diverse cellular mechanism(s) are involved in cancer promotion and progression, it is challenging to elucidate various underlying mechanisms. The intense research to study the diverse nature of cancer initiation and development with the associated risk factors and modulators has resulted in innumerable molecular and cellular markers specific to different cancer types. Almost all the exogenous compounds entering the cells are metabolized by enzymes of phase I and phase II. During biotransformation of any pro-carcinogens and other xenobiotics, the activation of phase I and suppression of phase II enzymes are required to exert their mutagenic, toxic, or carcinogenic effect. Metabolic activation, detoxification, cellular proliferation, programmed cell death, angiogenesis, and metastasis have been involved in target-specific pathways leading to oncogenic mechanisms elucidation. The interaction of parent xenobiotics with a particular target can either positively, negatively, or neutrally influence their respective cellular pathways. In the study, biotransformation by CYP450 isozymes, detoxification by GST (glutathione S-transferase) and NAT (N-acetyltransferase) isozymes, DNA adduction formation, and (dibenzo[a,l]pyrene) DBP-mediated cell proliferation have been comprehensively reviewed.

**Introduction**

Mammary cancer (MC) is the most commonly diagnosed cancer and the primary cause of cancer death in females worldwide. About 85% of malignancy occurs in mammary ducts, and about 15% arises in mammary glandular tissues. Primarily asymptomatic tumor growth is originated in mammary ducts and lobules, having a reduced chance of metastasis. It may spread from surrounding tissues to the breast lymph nodes and other distant body organs as time passes. The latter is the leading cause of the mortality of women worldwide. About 2.3 million individuals suffer from MC, in which more than 6 lakh deaths were recorded in 2020. Moreover, about 7.8 million women having MC for the last five years succeeded in their lives by the end of 2020. Compared to other cancers, maximum ‘disability-adjusted life years (DALYs)’ are seen in the women population suffering from MC, making it one of the most predominant malignancies globally. However, the advancements of sophisticated tools and techniques and systematic

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implications of early detection programs starting at the beginning of 1980 curtail about 40% of cases by 2020 in socio-economically privileged countries. Although, such countries can drop mortality rates between 2-4% annually. If an annual reduction of 2.5% attains globally, 2.5 million deaths could be curtailed by 2040.\textsuperscript{1,5}

MC is a non-communicable disease, and no relation links its progression and development with bacterial and/or viral infection, unlike cervical cancer and human papillomavirus (HPV) infection. There are no substantial risk factors in almost 50% of cases rather than gender and age above 40 years. Major risk factors accountable for MC progression development include family history, obesity, alcohol, overage, prolonged exposure to radiation and environmental pollution, pregnancy at later age just before the onset of menopause, tobacco smoking, and hormonal therapy after menopause. Avoidance of all lifestyle risk factors can reduce the chance of developing MC up to 30%.\textsuperscript{6-8} According to the International Agency for Research on Cancer (IARC), the cases of all types of cancer may be two folds by 2070 in comparison to 2020 if occurrence persists with the current rate especially shown by socio-economic backward countries. If countries fail to implement advanced planning and novel strategies to prevent and control the disease, it may be resulted in an annual increment of 34 million new patients by 2070.\textsuperscript{9}

**Carcinogens**

Cancer-causing agents are generally known as carcinogens. Chemical compounds categorized as a carcinogen does not mean that it will induce cancer. Certain factors cumulatively put the population prone to developing cancer ahead depending on carcinogen exposure and their genetic instability. Carcinogens may increase cancer risk by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes, and induces the uncontrolled, malignant division, ultimately leading to tumor formation. Usually, if too severe to repair, DNA damage leads to programmed cell death, but if the programmed cell death pathway is damaged, it cannot prevent itself from becoming a cancer cell.\textsuperscript{10} Chemical carcinogens may be genotoxic or nongenotoxic. Genotoxic agents usually refer to carcinogens that either directly bind to or damage genomic DNA, resulting in mutations exerting tumor-promoting activity. Nongenotoxic carcinogens are characterized by promoting activity, hormone modifying, immunosuppressive, cytotoxic, or peroxisome proliferating activity.

**Classification of Carcinogens**

According to the IARC, chemical compounds have been classified into four groups: Group 1) compounds or mixtures of this group are carcinogenic to humans. The exposure circumstance entails carcinogenic exposures to humans; Group 2A) Compounds or mixtures are probably carcinogenic to humans. The exposure circumstance entails directions that are probably carcinogenic to humans; Group 2B) Chemical agents having minimum possibilities for inducing carcinogenic properties in the human population; Group 3) Compounds or mixtures are not carcinogenic.\textsuperscript{11} According to the National Toxicology Program (NTP), the U.S. Department of Health and Human Services categorizes carcinogens into two groups. The first one deals with compounds known as a human carcinogens, and the second one contains chemical agents rationally expected to be a human carcinogen\textsuperscript{12}

**Dibenzo[a,l]pyrene**

The scrupulous evidence on dibenzo[a,l]pyrene (DBP) and its prevalence to induce cancer have been reported. DBP is a yellow-red odorless crystal classified as group 2A and experimentally estimated human carcinogen by IARC and NTP.\textsuperscript{13,14} It is mainly formed due to inefficient combustion of fossil fuels, charcoals, tobacco products, vaping chemicals, woods, plastic wares, and bones. Structurally DBP (CID:
9119) is a six-ring polycyclic aromatic hydrocarbon and its related fifty-two designated synonyms known in the PubChem database. Structurally DBP shows two grooves, respectively known as bay and fjord regions (Figure 1). Intermediates formed due to the latter groove are more susceptible to carcinogenic activities.  

**Figure 1:** Chemical structure of DBP. The numbering shows positions that can form intermediates during bioactivation.

**Biotransformation of DBP**
Genotoxic, mutagenic, and cancer-inducing properties of DBP have been established well by various *in vitro* and *in vivo* experiments. Biotransformation of DBP to DNA-reactive intermediates includes metabolic activation to either diol epoxides through CYP-dependent monoxygenases and epoxide hydrolases or receptive metabolites via an electron oxidation pathway. DBP has been demonstrated to be metabolized by CYP1A1, 1A2, 1B1, 2B6, and 2C9 in cell-free systems and in addition MCF-7 cells to diastereomeric 11,12-diol-13,14-epoxides (Figure 2). DBP is initially oxidized into dibenzo[a,l]pyrene-11,12-epoxide using diverse cytochrome CYP450s followed by formation of dibenzo[a,l]pyrene-11,12-diol. Further, it is oxidized into an ultimate carcinogenic intermediate dibenzo[a,l]pyrene-11,12-diol-13,14-epoxide via numerous CYP450s.

**Figure 2:** Formation and absolute stereochemistry of DBP metabolites responsible for the carcinogenicity of the parent compound. Solid arrows depict the preferred metabolic pathway.
Cytochrome P450 Isozymes
CYP450s are major metabolizing enzymes drawing significant consideration by researchers across the globe due to their significant role in the bioactivation of chemical compounds, including environmental pollutants, food additives, drug molecules, mutagens, carcinogens, and adulterants, followed by detoxification via second phase metabolizing enzymes and thus excrete out undesired intermediates formed during metabolic activation of parent compounds. Most of the PAHs produce carcinogenic metabolites upon bioactivation via CYP450s. Moreover, almost seventy percent of bioactivation of xenobiotics undergoes via CYP450 isozymes (Figure 3).

Figure 3: Percentage-wise contribution of CYP450s in metabolic bioactivation of PAHs. Most of the studies reveal that biotransformation of DBP into its carcinogenic metabolite undergoes CYP1A1, 1A2, and 1B1. The cellular fate of DBP as a mammary carcinogen is shown in Figure 4.

Aryl Hydrocarbon Receptor-Mediated Bioactivation
Aryl hydrocarbon receptor (AhR) plays a key role in DBP bioactivation akin to other PAHs. Coupling of DBP activates AhR resulting in its separation from its complex binding entities e.g., heat shock protein 90, aryl hydrocarbon receptor-interacting protein, and coactivator of Hsp90/70-chaperone system, thereby facilitation of its movement inside the nucleus. Further, the complex AhR-DBP couples to AhR nuclear translocator, and thus resulting complex is activated via C-terminus phosphorylation of tyrosine residue. AhR-ARNT complex finds xenobiotic response elements on promoter sites of respective CYP450 isozymes to mitigate their genes. CYP1A1, 1A2, 1B1 genes are modulated via the molecular interaction of different coactivators and transcription-regulating factors.

Figure 4. The cellular fate of DBP as a mammary carcinogen.
Detoxification of DBP

The balance between the metabolic activation and several detoxification processes influences the intracellular level of diol-epoxide-DNA-adduct formation. Since the sterically hindered bay-region diol-epoxides show an apparent low affinity for microsomal epoxide hydrolase and their half-lives are substantially increased by a stabilization effect of intracellular lipids, the spontaneous and enzymatic catalyzed hydrolysis to less toxic tetraols appear to be of minor importance in the cellular defense against diol-epoxides appear to be the glutathione S-transferase catalyzed conjugation with glutathione.\textsuperscript{33-35}

GSTs are involved in the metabolism of a variety of xenobiotic compounds, including DBP. These enzymes catalyze the conjugation of diverse electrophilic compounds with glutathione, giving rise in most cases to less reactive, water-soluble metabolites that are readily excreted. In humans, four classes of cytosolic GST isozymes (α, μ, π and θ) have thus far been identified, and several of them are polymorphic. Several epidemiological studies have investigated the association of GST genetic polymorphisms with breast cancer risk. Charred meat intake and cigarette smoking are the primary sources of PAH exposure in humans. Some epidemiological studies have suggested that these two lifestyle factors may be associated with the risk of breast cancer.\textsuperscript{36-40}

The differences in the activity and enantioselectivity of DBP metabolites depend on their geometry and absolute configuration. For example, the stereoisomeric bay-region diol-epoxides, particularly the syn-diastereomers, were in most cases efficiently conjugated by human GST of class μ (GSTM) wide variations in enantioselectivity ranging from 50-90%. In contrast, human GST of class π showed in most cases only an appreciable activity towards bay-region anti-diol-epoxides and a high preference for conjugation of enantiomers with (R, S, S, R)-configuration.\textsuperscript{41-43}

Apart from GST isozymes, another essential phase II enzyme, Arylamine N-acetyltransferase (NAT), plays an essential role in detoxifying heterocyclic amines and other xenobiotics. These cytosolic enzymes are present in eukaryotes and prokaryotes. Humans have two isozymes of arylamine N-acetyltransferases (NAT1 and NAT2) that are 81% homologous but differ in their tissue distribution and substrate specificity. The slow NAT2 acetylation phenotypes have shown a relationship to urinary bladder cancer. However, NAT polymorphisms linked to colon, breast, lung, and prostate cancers are more controversial.\textsuperscript{44-50}
Previous computational study shows the order of binding interaction of GSTP1, GSTM1, and GSTA1 with (-)-anti-DBPDE, contrary to the wet-lab findings that emphasized the major enzymatic activity of GSTA1. However, there are no major differences reflected in the above in silico findings. It means that (-)-GSTA1, GSTM1, or GSTP1 might conjugate (-)-anti-DBPDE. Furthermore, GSTA1, A2, A3, A4, and A5 (A1>A3>A4>A2>A5) also showed plausible binding activity with (-)-anti-DBPDE, which is nearly close to experimental data.\textsuperscript{51-54} In the case of (+)-syn-DBPDE, the binding propensity of GSTM1 was found greater than GSTP1 and GSTA1, which is somewhat similar to the wet-lab findings. Moreover, previous findings exhibited a similar molecular interaction of GSTA1 with both (-)-anti-DBPDE and (+)-syn-DBPDE. Despite above, molecular interaction of GSTA1, M1 and P1 with (+)-anti-DBPDE (GSTA1>M1>P1) and (-)-syn-DBPDE (GSTM2>A4>P1) is different and showed comparatively low activity. The binding affinity of NAT2 is consistent and greater NAT1 in either (±)-anti-DBPDE or (±)-syn-DBPDE agreed to the experimental data.\textsuperscript{51,52}

**DNA adduct formation by diol-epoxides of DBP**

DBP diol-epoxides (DBPDEs) form adducts with nucleic acids and proteins via covalent interactions. The adduct formation occurs due to benzylc oxiranyl carbon with exocyclic amino residues dG (deoxyguanosine) and dA (deoxyadenosine). Previous studies show that diol-epoxides of bay regions showing affinity towards N2-amino residue of dG while fjord-region intermediates form N6-amino residue of dA. For example, (+)-anti-BPDE, a bay-region metabolite, exhibits more than ninety percent affinity to form adducts with dG, while (-)-anti-DBPDE a fjord-region metabolite form more than seventy-five percent adducts with dA adducts. DNA adduct formation with both bay- and fjord-region intermediates is due to their structural variation.\textsuperscript{55-64} DBP diol-epoxide intermediates viz., (±)-anti-DBPDE and (±)-syn-DBPDE do not form N6-dA adduct. The preferential adduct formation is shown with dT and dG. The cis-and trans- (-)-anti-DBPDE and (+)-syn-DBPDE depicted similar results as above. Structurally the cis-product is less flexible than the trans-intermediates as cis-position shows sterically crowded two hydroxyl groups at the similar site of the benzylc ring while in trans-position, both hydroxy groups are located at opposite sides. Diol-epoxide-derived product can be relative to the major or minor groove of DNA helical structure depending upon the structural configuration viz, cis or trans, and dA or dG base preference. Previous in silico study shows that N6-dA adduct with trans-(-)-anti-DBPDE, and N6, N7-dA adduct is formed with cis-(-)-anti-DBPDE, trans-(±)-syn-DBPDE, and cis-(±)-syn-DBPDE supporting experimental findings determined so far.\textsuperscript{65-71} Moreover, Ahmad KMK et al., 2020 also predicted that the tendency of binding interactions of DBPDEs with DNA is more remarkable than molecular targets of NER pathways concluding that inadequate removal or partial repair of bulky adducts might undergo due to their weak binding forces. The substantial binding of DBPDEs with DNA supports more chemical adduct formation than its removal or repair.\textsuperscript{65} The molecular interaction of various diastereomeric metabolites of DBP with DNA is shown in Figure 6.
Figure 6: Molecular interactions of DNA with a) (-)-anti-DPBDE, b) (+)-anti-DPBDE, c) (-)-syn-DPBDE, d) (+)-syn-DPBDE, e) trans-derivative of (-)-anti-DBPDE, f) cis-derivative of (-)-anti-DBPDE, g) trans-derivative of (+)-syn-DBPDE, h) cis-derivative of (+)-syn-DBPDE.

DBP-Mediated Cell Proliferation

Typically, apoptosis occurs via mitochondrial or intrinsic pathway facilitating through proteins of the Bcl-2 family when any gets stressed. Various members of this family having antiapoptotic properties regulates complex programmed cell death phenomenon. The survival or death of a cell depends upon the balance between proapoptotic and antiapoptotic proteins. Dysregulation of BAX or upregulation of Bcl-2 and Bcl-XL hinders apoptosis or vice versa. One of the crucial nuclear protein p53 translocate to mitochondria and interacts with antiapoptotic proteins viz., Bcl-2 and Bcl-XL thereby facilitating apoptosis. It may induce programmed cell death by interacting with ARAF1, a key member of apoptosome complex, via activation of Caspase-9. Dysregulation of p53 may hamper the control over cell cycle mechanism, suppressing critical regulators of proapoptotic pathways. Deactivation of RB protein leads to the activation and release of E2F, thereby inducing the expression of P14ARF, a negative regulator of MDM2. The MDM2 itself is a negative regulator of p53, inhibition of the former increases the expression of the latter resulting occurrence of programmed cell death. Moreover, E2F protein may activate the Bcl-2 and CASPASE family members via cascaded molecular interactions. Moreover, Khan et al., 2018 predicted the molecular binding interactions of DBPDEs with CASPASES, BAX, Bcl-2, MDM2, p53, p53-MDM2 complex, p21, p16, CyclinD1-CDK4 complex, CyclinE1-CDK2 complex, H-
Ras, K-Ras, BRCA1, and BRCA2. They exhibited the strong binding of Caspase-9 compared to Caspase-8 and Caspase-3 with (-)-anti-DBPDE and (+)-syn-DBPDE. Caspase-9 and Apaf-1 activate the protease that isolates and activates Caspase-3 and thereby execution of apoptosis. Nevertheless, it may be possible that due to solid interaction, the unavailability of Caspase-9 hampering the reaction with Apaf-1 that may inhibit apoptosis. Further, the strong interaction of DBPDEs with p53 and weak binding with p21, a downstream target of p53 and CDKs inhibitor, p16, a negative regulator of the cell cycle, leads towards suppression of their expected functionalities. It means that dysregulation of cell cycle checkpoints succeeds towards abnormal cellular proliferation, growth, and development of oncogenic cells.\cite{95}

**Conclusion**

The review deals with the structural insight into the molecular mechanism of DBP bioactivation and thereby inducing mammary carcinogenesis through integrated binding interactions with various molecular targets of various cellular pathways. Moreover, Lead molecules with electron-rich properties easily bind with the target proteins and receptors in organisms through various chemical forces, thereby holding numerous applications in drug discovery. The review is helpful to understand the structural insight of PAHs and thus facilitating designing of novel leads with negligible toxicity besides searching and identifying anti-cancer agents from existing libraries that can suppress the activity of molecular target(s) involved in DBP-induced mammary carcinogenesis through the amalgamation of *in silico* and *in vitro* experimentations.

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**Conflicts of Interest**

The authors declare that there are no conflicts of interest relevant to this article.

**References**

1. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International Variation in Female Breast Cancer Incidence and Mortality Rates. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1495–506.
2. Ginsburg O, Yip C, Brooks A, Cabanes A, Caleffi M, Dunstan Yataco JA, et al. Breast cancer early detection: A phased approach to implementation. Cancer. 2020;126(S10):2379–93.
3. Velazquez Berumen A, Jimenez Moyao G, Rodriguez NM, Ilbawi AM, Migliore A, Shulman LN. Defining priority medical devices for cancer management: a WHO initiative. Lancet Oncol. 2018;19(12):e709–19.
4. Ilbawi AM, Velazquez-Berumen A. World Health Organization List of Priority Medical Devices for Cancer Management to Promote Universal Coverage. Clin Lab Med. 2018;38(1):151–60.
5. Rositch AF, Unger-Saldaña K, DeBoer RJ, Ng'ang'a A, Weiner BJ. The role of dissemination and implementation science in global breast cancer control programs: Frameworks, methods, and examples. Cancer. 2020;126(S10):2394–404.
6. Wild CP, E W, Stewart BW. World cancer report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer. World Health Organization. 2020. 15-91.
7. Barrios CH, Reinert T, Werutsky G. Global Breast Cancer Research: Moving Forward. Am Soc Clin Oncol Educ B. 2018;(38):441–50.
8. Azamjah N, Soltan-Zadeh Y, Zayeri F. Global Trend of Breast Cancer Mortality Rate: A 25- Birkett N, Al-Zoughool M, Bird M, Baan RA, Zielinski J, Krewski D. Overview of biological mechanisms of human carcinogens. J Toxicol Environ Heal Part B. 2019;22(7–8):288–359.
9. Soerjomataram I, Bray F. Planning for tomorrow: global cancer incidence and the role of prevention 2020-2070. Nat Rev Clin Oncol 2021; Jun 2; 1-10
10. Birkett N, Al-Zoughool M, Bird M, Baan RA, Zielinski J, Krewski D. Overview of biological mechanisms of human carcinogens. J Toxicol Environ Heal Part B. 2019;22(7-8):288-359.
11. Barupal DK, Schubauer-Berigan MK, Korenji M, Zavadil J, Guyton KZ. Prioritizing cancer hazard assessments for IARC Monographs using an integrated approach of database fusion and text mining. Environ Int. 2021;156:106624.
12. Rodu B, Cole P, Mandel JS. Evaluation of the National Toxicology Program Report on Carcinogens. Regul Toxicol Pharmacol. 2012. 64(1):186-8.
13. Goodman JE, Mayfield DB, Becker RA, Hartigan SB, Erraguntla NK. Recommendations for further revisions to improve the International Agency for Research on Cancer (IARC) Monograph program. Regul Toxicol Pharmacol. 2020;113:104639.
14. Suarez-Torres JD, Alzate JP, Orjuela-Ramirez ME. The NTP Report on Carcinogens: A valuable resource for public health, a challenge for regulatory science. J Appl Toxicol. 2020;40(1):169-75.
15. Identification of Potential Lead Molecules against Dibenzo[a,l]pyrene-induced Mammary Cancer through Targeting Cytochrome P450 1A1, 1A2, and 1B1 Isozymes. Biointerface Res Appl Chem. 2021;12(1):1096-109.
16. Arif J. Microsome-mediated bioactivation of dibenzo[a,l]pyrene and identification of DNA adducts by 32P-postlabeling. Carcinogenesis. 1997;18(10):1999–2007.
17. Khan MKA, Akhtar S, Arif JM. Development of In Silico Protocols to Predict Structural Insights into the Metabolic Activation Pathways of Xenobiotics. Interdiscip Sci Comput Life Sci. 2018;10(2):329–45.
18. Gupta RC, Arif JM, Gairola CG. Enhancement of pre-existing DNA adducts in rodents exposed to cigarette smoke. Mutat Res Mol Mech Mutagen. 1999;424(1-2):195−205.
19. Smith JN, Mehinagic D, Nag S, Crowell SR, Corley RA. In vitro metabolism of benzo[a]pyrene-7,8-dihydridiol and dibenzo[def,p]chrysene-11,12 diol in rodent and human hepatic microsomes. Toxicol Lett. 2017;269:23−32.
20. Smith WA, Arif JM, Gupta RC. 1,2-dithiole-3-thione and its structural analogue oltipraz are potent inhibitors of dibenzo[a,l]pyrene-DNA adduction in female Sprague-Dawley rats. Int J Cancer. 2001;91(1):132–6.
21. Chen K-M, Guttenplan JB, Zhang S-M, Aliaga C, Cooper TK, Sun Y-W, et al. Mechanisms of oral carcinogenesis induced by dibenzo[a,l]pyrene: An environmental pollutant and a tobacco smoke constituent. Int J Cancer. 2013;133(6):1300−9.
22. Shou M, Krausz KW, Gonzalez FJ, Gelboin H V. Metabolic activation of the potent carcinogen dibenzo[a,l]pyrene by human recombinant cytochromes P450, lung and liver microsomes. Carcinogenesis. 1996;17(11):2429−33.
23. Siddens LK, Bunde KL, Harper TA, McQuistan TJ, Lohr C V, Bramer LM, et al. Cytochrome P450 1b1 in polycyclic aromatic hydrocarbon (PAH)-induced skin carcinogenesis: Tumorigenicity of individual PAHs and coal-tar extract, DNA adduction and expression of select genes in the Cyp1b1 knockout mouse. Toxicol Appl Pharmacol. 2015;287(2):149−60.
24. Siddens LK, Larkin A, Krueger SK, Bradfield CA, Waters KM, Tilton SC, et al. Polycyclic aromatic hydrocarbons as skin carcinogens: Comparison of benzo[a]pyrene, dibenzo[def,p]chrysene and three environmental mixtures in the FVB/N mouse. Toxicol Appl Pharmacol. 2012;264(3):377−86.
25. Manikandan P, Nagini S. Cytochrome P450 Structure, Function and Clinical Significance: A Review. Curr Drug Targets. 2018;19(1):38−54.
26. Munro AW, McLean KJ, Grant JL, Makris TM. Structure and function of the cytochrome P450 peroxigenase enzymes. Biochem Soc Trans. 2018;46(1):183−96.
27. Barnaba C, Gentry K, Sumangala N, Ramamoorthy A. The catalytic function of cytochrome P450 is entwined with its membrane-bound nature. F1000Research. 2017;6:662.
28. Rendic SP, Guengerich FP. Human Family 1–4 cytochrome P450 enzymes involved in the metabolic activation of xenobiotic and physiological chemicals: an update. Arch Toxicol. 2021;95(2):395−472.
29. Shimada T, Guengerich FP. Inhibition of Human Cytochrome P450 1A1-, 1A2-, and 1B1-Mediated Activation of Procarcinogens to Genotoxic Metabolites by Polycyclic Aromatic Hydrocarbons. Chem Res Toxicol. 2006;19(2):288–94.
30. Smith JN, Mehinagic D, Nag S, Crowell SR, Corley RA. In vitro metabolism of benzo[a]pyrene-7,8-dihydrodiol and dibenzo[def,p]chrysene-11,12 diol in rodent and human hepatic microsomes. Toxicol Lett. 2017;269:23–32.
31. Nakano N, Sakata N, Katsu Y, Nochise D, Sato E, Takahashi Y, et al. Dissociation of the AhR/ARNT complex by TGF-β/Smad signaling represses CYP1A1 gene expression and inhibits benzo[a]pyrene-mediated cytotoxicity. J Biol Chem. 2020;295(27):9033–51.
32. Androutsopoulos VP, Tsatsakis AM, Spandidos DA. Cytochrome P450 CYP1A1: wider roles in cancer progression and prevention. BMC Cancer. 2009;9(1):187.
33. Sayer JM, Yagi H, van Bladeren PJ, Levin W, Jerina DM. Stereoselectivity of microsomal epoxide hydrolase toward diol epoxides and tetrahydroepoxides derived from benz[a]anthracene. J Biol Chem. 1985;260(3):1630–40.
34. Dock L, Waern F, Martinez M, Grover PL, Jernström B. Studies on the further activation of benzo[a]pyrene diol epoxides by rat liver microsomes and nuclei. Chem Biol Interact. 1986;58(C):301–18.
35. Jernström B, Mannervik B, Funk M, Seidel A. Glutathione Transferase A1-1 Catalyzed Conjugation of Polycyclic Aromatic Hydrocarbon Diol-Epoxides with Glutathione. Polycycl Aromat Compd. 1996;10(1–4):51–7.
36. Hengstler JG, Arand M, Herrero ME, Oesch F. Polymorphisms of N-Acetyltransferases, Glutathione S-Transferases, Microsomal Epoxide Hydrolase and Sulfotransferases: Influence on Cancer Susceptibility. In: Recent results in cancer research. Fortschritte der Krebsforschung Progrès dans les recherches sur le cancer. 1998. p. 47–85.
37. Mitrunen K, Jourenkova N, Kataja V, Eskelinen M, Kosma VM, Benhamou S, et al. Glutathione S-transferase M1, M3, P1, and T1 genetic polymorphisms and susceptibility to breast cancer. Cancer Epidemiol Biomarkers Prev. 2001;10(3):229–36.
38. Song Z, Shao C, Feng C, Lu Y, Gao Y, Dong C. Association of glutathione S-transferase T1, M1, and P1 polymorphisms in the breast cancer risk: a meta-analysis. Ther Clin Risk Manag. 2016;12:763.
39. Park HL. Epigenetic Biomarkers for Environmental Exposures and Personalized Breast Cancer Prevention. Int J Environ Res Public Health. 2020;17(4):1181.
40. Birkett N, Al-Zoughool M, Bird M, Baan RA, Zielinski J, Krewski D. Overview of biological mechanisms of human carcinogens. J Toxicol Environ Heal Part B. 2019;22(7-8):288–359.
41. Sundberg K, Dreij K, Seidel A, Jernström B. Glutathione Conjugation and DNA Adduct Formation of Dibenzo[a,l]pyrene and Benzo[a]pyrene Diol Epoxides in V79 Cells Stably Expressing Different Human Glutathione Transferases. Chem Res Toxicol. 2002;15(2):170–9.
42. Sundberg K. Differences in the catalytic efficiencies of allelic variants of glutathione transferase P1-1 towards carcinogenic diol epoxides of polycyclic aromatic hydrocarbons. Carcinogenesis. 1998;19(3):433–6.
43. Fields WR, Morrow CS, Doss AJ, Sundberg K, Jernström B, Townsend AJ. Overexpression of Stably Transfected Human Glutathione S-Transferase P1–1 Protects against DNA Damage by Benzo[a]pyrene Diol-Epoxide in Human T47D Cells. Mol Pharmacol. 1998;54(2):298–304.
44. Endo Y, Yamashita H, Takahashi S, Sato S, Yoshimoto N, Asano T, et al. Immunohistochemical determination of the miR-1290 target arylamine N-acetyltransferase 1 (NAT1) as a prognostic biomarker in breast cancer. BMC Cancer. 2014;14(1):990.
45. Li P, Butcher NJ, Minchin RF. Effect arylamine N-acetyltransferase 1 on morphology, adhesion, migration, and invasion of MDA-MB-231 cells: role of matrix metalloproteinases and integrin αV. Cell Adh Migr. 2020;14(1):1–11.
46. Carlisle SM, Trainor PJ, Doll MA, Stepp MW, Klinge CM, Hein DW. Knockout of human arylamine N-acetyltransferase 1 (NAT1) in MDA-MB-231 breast cancer cells leads to increased reserve capacity, maximum mitochondrial capacity, and glycolytic reserve capacity. Mol Carcinog. 2018;57(11):1458–66.

47. Vineis P, Bartsch H, Caporaso N, Harrington AM, Kadlubar FF, Landi MT, et al. Genetically based N-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. Nature. 1994;369(6476):154–6.

48. Hein DW. Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. Mutat Res Mol Mech Mutagen. 2002;506–507:65–77.

49. Wang T, Marei HE. Landscape of NAT2 polymorphisms among breast cancer. Biomed Pharmacother. 2016;77:191–6.

50. Carlisle S, Hein D. Retrospective analysis of estrogen receptor 1 and N-acetyltransferase gene expression in normal breast tissue, primary breast tumors, and established breast cancer cell lines. Int J Oncol. 2018;53(2):694–702.

51. Jernström B, Funk M, Steinbrecher T, Seidel A. Glutathione Transferase Catalyzed Conjugation of Diol Epoxides Derived from Polycyclic Aromatic Hydrocarbons with Glutathione. Polycycl Aromat Compd. 1993;3(4):213–9.

52. Drejik K, Sundberg K, Johansson A-S, Nordling E, Seidel A, Persson B, et al. Catalytic Activities of Human Alpha Class Glutathione Transferases toward Carcinogenic Dibenzo[a,l]pyrene Diol Epoxides. Chem Res Toxicol. 2002;15(6):825–31.

53. McCarty KM, Santella RM, Steck SE, Cleveland RJ, Ahn J, Ambrosone CB, et al. PAH–DNA Adducts, Cigarette Smoking, GST Polymorphisms, and Breast Cancer Risk. Environ Health Perspect. 2009;117(4):552–8.

54. Khan MKA, Akhtar S, Al-Khodairy F. Molecular docking approach to elucidate metabolic detoxification pathway of polycyclic aromatic hydrocarbons. NeuroPharmac J. 2021; 6(1): 150-161.

55. Hargis JC, Schaefer HF, Houk KN, Wheeler SE. Noncovalent interactions of a benzo[a]pyrene diol epoxide with DNA base pairs: insight into the formation of adducts of (+)-BaP DE-2 with DNA. J Phys Chem A. 2010;114(4):2038–44.

56. Ewa B, Danuta M-Š. Polycyclic aromatic hydrocarbons and PAH-related DNA adducts. J Appl Genet. 2017;58(3):321–30.

57. Genies C, Jullien A, Lefebvre E, Revol M, Maitre A, Douki T. Inhibition of the formation of benzo[a]pyrene adducts to DNA in A549 lung cells exposed to mixtures of polycyclic aromatic hydrocarbons. Toxicol Vitr. 2016;35:1–10.

58. Motwani H V., Westberg E, Törnvqvist M. Interaction of benzo[a]pyrene diol epoxide isomers with human serum albumin: Site specific characterization of adducts and associated kinetics. Sci Rep. 2016;6(1):36243.

59. Cai Y, Ding S, Geacintov NE, Broyde S. Intercalative Conformations of the 14 R (+)- and 14 S (−)- trans-anti-DBa[,]P-N 6-dA Adducts: Molecular Modeling and MD Simulations. Chem Res Toxicol. 2011;24(4):522–31.

60. Shiizaki K, Kawanishi M, Yagi T. Modulation of benzo[a]pyrene–DNA adduct formation by CYPI inducer and inhibitor. Genes Environ. 2017;39(1):14.

61. Lukashevich O V, Baskunov VB, Darii M V., Kolbanovskiy A, Baykov AA, Gromova ES. Dnm3a-CD Is Less Susceptible to Bulky Benzo[a]pyrene Diol Epoxide-Derived DNA Lesions Than Prokaryotic DNA Methyltransferases. Biochemistry. 2011;50(5):875–81.

62. Dipple A, Pigott MA, Agarwal SK, Yagi H, Sayer JM, Jerina DM. Optically active benzo[c]phenanthrene diol epoxides bind extensively to adenine in DNA. Nature. 1987;327(6122):535–6.

63. Arif JM, Smith WA, Gupta RC. Tissue distribution of DNA adducts in rats treated by intramammillary injection with dibenzo[a,l]pyrene, 7,12-dimethylbenz[a]anthracene and benzo[a]pyrene. Mutat Res Mol Mech Mutagen. 1997;378(1–2):31–9.

64. Khan MKA, Akhtar S, Arif JM. Development of In Silico Protocols to Predict Structural Insights into the Metabolic Activation Pathways of Xenobiotics. Interdiscip Sci Comput Life Sci. 2018;10(2):329–45.
65. Ahmad KMK, Salman A, Al-Khodairy Salman F, Al-Marshad Feras M, Alshahrani Abdulrahman M, Arif Jamal M. Computational Exploration of Dibenzo[a,l]Pyrene Interaction to DNA and its Bases: Possible Implications to Human Health. Biointerface Res Appl Chem. 2020;11(4):11272–83.
66. Dreij K, Seid E, Jernström B. Differential Removal of DNA Adducts Derived from anti-Diol Epoxides of Dibenzo[a,l]pyrene and Benzo[a]pyrene in Human Cells. Chem Res Toxicol. 2005;18(4):655–64.
67. Ruan Q, Kolbanovskiy A, Zhuang P, Chen J, Krzeminski J, Amin S, et al. Synthesis and Characterization of Site-Specific and Stereosymmetric Fjord Dibenzo[a,l]pyrene Diol Epoxide-N 6-Adenine Adducts: Unusual Thermal Stabilization of Modified DNA Duplexes. Chem Res Toxicol. 2002;15(2):249–61.
68. Zhong Q, Amin S, Lazarus P, Spratt TE. Differential repair of polycyclic aromatic hydrocarbon DNA adducts from an actively transcribed gene. DNA Repair (Amst). 2010;9(9):1011–6.
69. Shafirovich V, Kolbanovskiy M, Kropachev K, Liu Z, Cai Y, Terzidis MA, et al. Nucleotide Excision Repair and Impact of Site-Specific 5',8-Cyclopurine and Bulky DNA Lesions on the Physical Properties of Nucleosomes. Biochemistry. 2019;58(6):561-74.
70. Gelhaus SL, Harvey RG, Penning TM, Blair IA. Regulation of benzo[a]pyrene-mediated DNA- and glutathione-adduct formation by 2,3,7,8-tetrachlorodibenzo-p-dioxin in human lung cells. Chem Res Toxicol. 2011;24(1):89–98.
71. Cai Y, Geacintov NE, Brody S. Nucleotide Excision Repair Efficiencies of Bulky Carcinogen–DNA Adducts Are Governed by a Balance between Stabilizing and Destabilizing Interactions. Biochemistry. 2012;51(7):1486–99.
72. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol. 2020;21(2):85–100.
73. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol. 2020;21(2):85–100.
74. Kale J, Osterlund Ej, Andrews DW. BCL-2 family proteins: changing partners in the dance towards death. Cell Death Differ. 2018;25(1):65–80.
75. Czabotar PE, Lessene G, Strasser A, Adams JM. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat Rev Mol Cell Biol. 2014;15(1):49–63.
76. Warren CFA, Wong-Brown MW, Bowden NA. BCL-2 family isoforms in apoptosis and cancer. Cell Death Dis. 2019;10(3):177.
77. Bogner C, Kale J, Pogmore J, Chi X, Shamas-Din A, Fradin C, et al. Allosteric Regulation of BH3 Proteins in Bd-xl Complexes Enables Switch-like Activation of Bax. Mol Cell. 2020;77(4):901–912.
78. Ouyang L, Shi Z, Zhao S, Wang FT, Zhou TT, Liu B, et al. Programmed cell death pathways in cancer: a review of apoptosis, autophagy and programmed necrosis. Cell Prolif. 2012;45(6):487–98.
79. Jan R, Chaudhry G-S. Understanding Apoptosis and Apoptotic Pathways Targeted Cancer Therapeutics. Adv Pharm Bull. 2019;9(2):205–18.
80. Guo Z, Song T, Wang Z, Lin D, Cao K, Liu P, et al. The chaperone Hsp70 is a BH3 receptor activated by the pro-apoptotic Bim to stabilize anti-apoptotic clients. J Biol Chem. 2020;295(37):12900–9.
81. Huang K, O’Neill KL, Li J, Zhou W, Han N, Pang X, et al. BH3-only proteins target BCL-xl/MCL-1, not BAX/BAK, to initiate apoptosis. Cell Res. 2019;29(11):942–52.
82. Yin C, Knudson CM, Korsmeyer SJ, Dyke T Van. Bax suppresses tumorigenesis and stimulates apoptosis in vivo. Nature. 1997;385(6617):637–40.
83. Oda E, Noxa, a BH3-Only Member of the Bcl-2 Family and Candidate Mediator of p53-Induced Apoptosis. Science. 2000;288(5468):1053–8.
84. Oda K, Arakawa H, Tanaka T, Matsuda K, Tanikawa C, Mori T, et al. p53AIP1, a Potential Mediator of p53-Dependent Apoptosis, and Its Regulation by Ser-46-Phosphorylated p53. Cell. 2000;102(6):849–62.
85. Kracikova M, Akiri G, George A, Sachidanandam R, Aaronson SA. A threshold mechanism mediates p53 cell fate decision between growth arrest and apoptosis. Cell Death Differ. 2013;20(4):576–88.
86. Hegeman SA, Ghannouma H, Zhou L. Role of p53-Mediated Apoptosis in Limiting Metastasis. UF J Undergrad Res. 2020;21(2).
87. Soengas MS. Apaf-1 and Caspase-9 in p53-Dependent Apoptosis and Tumor Inhibition. Science. 1999;284(5411):156–9.
88. Soengas MS. Apaf-1 and Caspase-9 in p53-Dependent Apoptosis and Tumor Inhibition. Science. 1999;284(5411):156–9.
89. Duffy MJ, Synnott NC, Crown J. Mutant p53 in breast cancer: potential as a therapeutic target and biomarker. Breast Cancer Res Treat. 2018;170(2):213–9.
90. Irwin M, Marin MC, Phillips AC, Seelan RS, Smith DI, Liu W, et al. Role for the p53 homologue p73 in E2F-1-induced apoptosis. Nature. 2000;407(6804):645–8.
91. Helin K, Harlow E, Fattaey A. Inhibition of E2F-1 transactivation by direct binding of the retinoblastoma protein. Mol Cell Biol. 1993;13(10):6501–8.
92. Christensen J. Characterization of E2F8, a novel E2F-like cell-cycle regulated repressor of E2F-activated transcription. Nucleic Acids Res. 2005;33(17):5458–70.
93. Nahle Z, Polakoff J, Davuluri R V., McCurrach ME, Jacobson MD, Narita M, et al. Direct coupling of the cell cycle and cell death machinery by E2F. Nat Cell Biol. 2002;4(11):859–64.
94. Akl H, Vervloesem T, Kiviluoto S, Bittremieux M, Parys JB, De Smedt H, et al. A dual role for the anti-apoptotic Bcl-2 protein in cancer: Mitochondria versus endoplasmic reticulum. Biochim Biophys Acta - Mol Cell Res. 2014;1843(10):2240–52.
95. Khan MKA, Akhtar S, Arif JM. Structural Insight into the Mechanism of Dibenzo[a,l]pyrene and Benzo[a]pyrene-Mediated Cell Proliferation Using Molecular Docking Simulations. Interdiscip Sci Comput Life Sci. 2018;10(4):653–73.

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