Identification of Anti-Cancer Compounds in Medicinal Plants Using Metabolomic Approaches: A Review

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Abstract *– The modern lifestyle despite its comfort has made cancer a second leading public health problem, following cardiovascular disease. As chemotherapeutic has many side effects including resistance, recent attention has focused on plants which may provide a good opportunity for complementary cancer treatment. Several studies have begun to focus on metabolomic research in order to discover the mechanisms of action of diverse medicinal plants, investigate biomarkers, and comprehend cancer progression at metabolic rates. This study aims to analyze and highlight related metabolomic investigations in medicinal plants that demonstrate the potential of biomarker compounds and their processes in cancer disease. The research methodology uses a literature review that is compiled from many connected journals. According to the findings, bioactive substances present in medicinal plants can be used as biomarkers to disrupt the metabolism of enzymes, transporters, and signaling pathways in cancer cells. Utilized analytical platforms include HPLC, GC-MS, FTIR and NMR. Statistical analysis employs the Anova, PCA, and OPLS-DA methods. Finally, we reviewed biomarkers of medicinal plants and metabolomic pathways, with the result that anticancer compounds may exert their activity by various methods affecting DNA replication, cell cycle, migration and apoptosis.*

Keywords: *anti-cancer, biomarkers, medicinal plant, metabolomic, review*

INTRODUCTION

According to the World Health Organization (2023), cancer is a category of disorder that can arise in practically any organ or tissue of the body when abnormal cells proliferate uncontrollably. Cancer is the second biggest cause of death, following cardiovascular disease. This is due to the fact that rapidly growing abnormal cells can travel to places other than where cancer cells originate, resulting in the formation of additional tumors and the death of cancer patients (Martin *et al.*, 2013). Treatment, procedures, and therapies such as targeted therapy, radiation, chemotherapy, and immunotherapy can all be used to cure cancer depending on the kind and stage of the disease. However, it has been discovered that the medicine might produce significant side effects due to its toxicity to the health of human cells (Derbal, 2018). Furthermore, chemotherapy and radiation therapy have poor side effects due to damage to normal cells, whereas immunotherapies and targeted therapies have a limited spectrum of targets and are expensive (Lemjabbar & Basbaum, 2022).

In recent years, there has been a rise in research focusing on the developmental novelty of anti-cancer compounds obtained from bioactive components recovered from natural ingredients and sources that have the power to greatly inhibit tumor growth and improve healing and survival (Kotecha *et al.*, 2016). Several epidemiological studies have found that eating bioactive plant components plays a vital role in the prevention of several chronic diseases (Mentella *et al.*, 2019). As a result, medicinal plants and herbal medicines are gaining interest due to their potential to treat serious diseases such as cancer (Sharifi-Rad *et al.*, 2019). According to Kim *et al.* (2021), medicinal plants and derivative substances can target cancer cells more efficiently and specifically without damaging normal cells. This is because the medicinal plants employed include various bioactive compounds, such as polyphenols, carotenoids, and glucosinolates, which alter the processes of differentiation, proliferation, apoptosis, and the halting of the cancer cell cycle (Singh & Yadav, 2022).

Metabolomics is a science that combines the science of biology, analytical chemistry, and bioinformatics to identify and quantify metabolites. In general, the metabolomic workflow consists of developing a research plan, preparing biological samples, analyzing using various instruments, processing and analyzing the data (Nusantara & Putri, 2018). Several metabolomics studies have been conducted to evaluate the link between carcinogenic metabolites in medicinal plants. The technique enables complete, unbiased, and high throughput analysis of medicinal plants with complex metabolite content. MS, NMR, and FTIR are commonly used metabolomics analysis methodologies that are paired with compound analysis tools such as GC or LC (Warsito, 2018). Oyonehi *et al.* (2021) used metabolomics to understand the mechanisms of traditional herbal medications against cancer. In addition, there is a study of the metabolomic perspective of medicinal plants for the treatment of gastrointestinal cancers (Guo *et al.*, 2022). Nonetheless, there are no publications that have thoroughly examined the use of metabolomic techniques to medicinal plants in the treatment of various forms of cancer in the human body. To fill the gap, this review will examine and highlight related metabolomic studies on medicinal plants as anti-cancer agents in diverse cancer types.

MATERIALS AND METHODS

All information collected from previously published data or research on medicinal plants that act as anti-cancer agents and are studied using metabolomic approaches, including samples, types of cancer, methods of analysis, statistical methods, biomarker identification results, and key points discovered. The research from every paper or publication that has been reviewed is accessible online through databases like MDPI, PubMed, Science Direct, Web of Science, and gray literature (Google Scholar). And it's found in a variety of keywords or phrases, such as metabolomics, medicinal plants, anti-cancer, in vitro, biomarkers, metabolite findings, platforms analysis and other. The deadline for data extraction from the journal is July 30, 2023.

RESULT AND DISCUSSION

Research so far has tested the cancer activity of medicinal plant compounds. Some of these plants and their compounds prove to be very effective against one or more types of cancers. The rest of the important medicinal plants shortlisted for their activities are presented in Table 1. along with their activities.

1. Cell Culture and Anti-Proliferative Assay

The study found that 28 different types of culturing cancer cells are used. MCF-7, A549, MDA-MB-231, HepG2, PC-3, HeLa, SKBR3, and A375 are the most prevalent types of cancer cells. In some countries, used cells are obtained from Type Culture Collection or Cell Banks. Following cell culture, media such as RPMI 1640, DMEM (Dulbecco's modified eagle's medium), glutamine, GlutaMax, and EDTA trypsin will be used, along with Fetal Bovine Serum (FBS) and penicillin streptomycin. Cell culture was grown at 37°C in a humidified 5% CO_2 environment. Furthermore, the anti-cancer activity of various medicinal plant extracts was determined in vitro utilizing the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) tests. This assay is used to determine which of the potential metabolites is responsible for the anti-cancer activity (Julca *et al.*, 2023). According to Scherlie (2011), MTT assays are one of the most commonly used methods for cytotoxicity screening due to their easy and quick approach.

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
1.	*Forsythia fructus*	B16-F10 cells	Melanoma cancer	UHPLC/QTOF-MS	Betulinic Acid	Betulinic acid could significantly increase the proportion of cells in G1 phase and reduced cell numbers S phase and G2/M	PCA OPLS-DA ANOVA	Bao *et al.*, 2018
					Forsythoside A	Forsythoside A showed antioxidant and antiinflammatory activities		
2.	*Vitis vinifera* L.	MSTO-211H (MSTO) cell line, MDA-MB-231(MDA) cell line, and PC3 cell line	Lung cancer, breast cancer	LC-HESI-HRMS	Proanthocyanidins	AGS induces pro-apoptosis effects by inhibiting	PCA ANOVA	Cuciniello *et al., 2022*
3.	*Annona muricata* L.	A549 cancer cells	Lung cancer	LC-MS/MS analysis	Pheophorbide A	Because pheophorbide A is a photosensitizing agent, it can confer resistance to certain anti-cancer medicines.	PCA OPLS-DA	Salac *et al.*, 2022

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
					Benzenoid, Diphenylcyclopropenone	This chemical can also be utilized as a cancer cell growth inhibitor		
4.	C. *spinosa* L. subsp. *rupestris* flower buds	T24 cells and Caco-2 cells	Carcinoma cancer, colorectal adenocarcinoma cancer	UHPLC-ESI/QTOF-MS	Polyphenols, Glucosinolates (Glucocapparin)	Glucosinolates, secondary metabolites known for their role in preventing disease and reducing the risk of carcinogenesis	Mann Whitney U test	Bacchetti *et al.*, 2022
5.	*Chamaecyparis obtusa* Leaf (Hinoki)	HCT116 cancer cell line	Colorectal cancer	GC-MS	Anthricin	Methanol extract of CO leaves had anti-proliferative activity against a human colorectal cancer cell line (HCT116)	PCA OPLS-DA	Kim *et al.*, 2015
6.	*Matricaria chamomilla*	HS27 cancer cell line, ZR-75 cancer cell lines	Breast cancer	2D NMR LC-HRMS	Chrysosplenetin, Apigenin	That chrysosplenetin (F2-ChE) and apigenin (F8-ChE) compounds from European fractions had anticancer activity against	PCA OPLS-DA	Atoum *et al.*, 2023
7.	*Citrus species*	A375 cell line, MCF cell line, A549 cell line, HaCat	Lung cancer, skin cancer, and breast cancer	GC-MS	Myo-inositol, Quinic acid, Aucubin, Doconexent	Citrus-derived nano and microvesicles reduce cancer cell proliferation, Grapefruit-derived	PCA OPLS-DA	Stanley *et al.*, 2020

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
						vesicles induce cell cycle arrest and affect the expression of oncogenes and cell-cycle regulatory genes in melanoma cells		
8.	*Curcuma longa* I.	4T1 cells	Breast cancer cachexia	1H-NMR	curcumin	Curcumin not only inhibits the proliferation of TNBC but also targets the NF-kB/UPS axis ameliorating muscle atrophy in TNBC-cachexia mice	PLS-DA	Zhang *et al.*, 2022
9.	*Glochidion velutinum* leaf extract	PC-3 cell line MCF-7 cell line	Prostate cancer, Breast cancer	LC-MS/MS-based	Epigallocatechin gallate, Ellagic acid, Isovitexin	Biomarker have anticancer activity against both prostate and breast cancer cell lines and might be responsible for the cytotoxic activities of *G. velutinum* extract and its bioactive fractions	PCA	Shah *et al.*, 2022
10.	*Hyphaene thebaica* leaves	HepG-2 cell line, A549 cell line, Vero cell line	Heart cancer, Lung cancer	HPLC	Phenolic, Flavonoids, Anthocyanins, Saponins	The content of these metabolites was positively correlated with the	PCA ANOVA	Taha *et al.*, 2020

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
						anticancer activity of some Saudi desert plants against HCC and breast carcinoma cell lines		
11.	*Spondias dulcis* leaf	A549 cell line	Lung cancer	LC-MS/MS based	Isokuersetin	Quercetin has an inhibitory role in A549 cell lung cancer Quercetin can suppress invasion and migration of cancer cells by inhibiting MMP-2 enzyme activity and expression Isoquercetin works by inhibiting cell growth (anti-proliferation) A549 lung cancer	OPLS-DA	Kuncoroyekti, 2022
12.	*Panax ginseng* root seedlings	MCF7 cell lines BV2 cell line	Breast cancer	GC-TOF-MS	Ginsenosides Rb1, Rg1, Rg3, and Rh2	GRg3 ⇒ can significantly reduce the inflammatory, GRh2 ⇒ has been reported to exhibit several beneficial biological effects such as anti-inflammatory, antioxidant, and	PCA OPLS-DA ANOVA	Sadiq *et al.*, 2023

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
						neuroprotective properties		
13.	*Citrus aurantifolia* (lime)	PLC/PRF/5 cell line	Liver cancer	LC-qTOF/MS GC-HRMS	Coumarins, Furanocoumarins, Limonoids, Flavonoids (hesperidin, limonin)	At 24h biomarker significantly induced apoptosis. The novel findings that the ethanolic extract of lime peel is more potent than the pure limonin and hesperidin compounds in anti-cancer effects	ANOVA	Phucharoenrak *et al.*, 2023
14.	*Manilkara zapota* and *Lansium domesticum* leaves	A549 cell line	Lung cancer	LC-MS/MS	Phenylpropanoids, Polyketides	The extract of both *M. zapota* and *L. domesticum* serve a promising antioxidant and anticancer agents	UNIFI software	Ruel Nacario *et al.*, 2022
15.	*Oldenlandia corymbosa* leaves	SKBR3 cell line	Breast cancer	LC-MS/MS UPLC/QTOF	Ursolic acids	This study revealed that ursolic acids causes mitotic catastrophe in cancer cells and identified three high-confidence protein binding targets by Cellular Thermal Shift Assay (CETSA)	PCA	Julca *et al.*, 2023

No.	**Specific medicinal plant treatment**	**Biological Sample**	**Cancer types**	**Analytical platform (s)**	**Biomarkers identified**	**Main findings**	**Statistical method**	**Ref**
16.	*Plicosepalus acacia* and *Plicosepalus curviflorus*	A549 cell line PC3 cell line A2780 cell line MDA-MB 231 cell line	Lung cancer, Prostate cancer, Ovarian cancer, Breast cancer	LC-ESI-TOF-MS/MS	Catechin, Sterol, Triterpenes, Delphinidin	Delphinidin was reported to prompt apoptosis in prostate cancer PC3 cell line by interfering with nuclear factor-kB signaling, Catechin was proven to possess an *in vitro* antiproliferative effect against the A549 lung cancer line by the inhibition of cyclin E1 and P-AKT and the induction	PCA ANOVA	Eltamany *et al.*, 2022
17.	*Caulerpa lentilifera*	HCT8 cell line, MCF7 cell line, Hep G2 cell line, KG-1a cell line, MDA-MB 231 cell line, MCF-10A cell line	Colorectal cancer, Breast cancer, Hepatic cancer, Leukemia	HPLC-ESI-HRMS/MS	Linolenic acid, Oleamide, Oleostearic, Palmitoleic acid, cafestol, Ouabain	Cafestol van curpress the rapid growth and migration pf cancer cells, Quabain is mainly used in the treatment of congestive heart failure and arrhythmias, and even as an anticancer agent in melanoma	Advanced Mass Spectral Database (M/Z cloud)	Nurkolis *et al.*, 2023
18.	*Eleutherine palmifolia*	HeLa cell line	Cervical cancer	UPLC-MS	Isoliquiritigenin, Oxyresveratrol	Isoliquiritigenin is able to inhibit cell proliferation and induce	Probit Analysis	Minggarwati, 2017

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
						apoptosis N16 melanoma cells		
19.	*Eleusine indica*	H1299 cell line MCF7 cell line SK-HEP-1 cell line	Breast cancer, Hepatic cancer	UHPLC-HRMS	Triacylglycerols, PhosphatidylcholineSphingomyelin, Ceramide	R-S5-C1-H1 affected the viability of H1299, MCF7, and SK-HEP-1 cell in dose and time dependent number	PCA OPLS-DA Heat map analysis	Puah *et al.*, 2022
20.	*Aloe vera*	Raji cells	Lymphoma cancer	1H NMR-MS	Aloin, Leucin	Aloin is an anthraquinone has been shown to possess anticancer potential activities, as it blocks signal transducers and s an activator of transcription 3 activation by inhibiting tumor angiogenesis and growth demonstrating its potential as a medicine candidate for cancer therapy	PLS-DA	Noorolahi *et al.*, 2016
21.	*Annona muricata* L.	HT29 cell line	Colon cancer	GC-TOF-MS	Tricosadiynoic acid	Amino acid metabolism, aerobic glycolysis, urea cycle and ketone bodies metabolism that contribute to	PCA	Daddiouaissa *et al.*, 2021

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
						energy metabolism and cancer cell proliferation.		
22.	*Crocus cancellatus* subsp. damascenus (Herb)	MDA-MB-231 cell line, MCF7 cell line	Breast cancer	GC-MS, LC-MS	Safranal, Crocin, Picrocrocin, Crocetin	Stigma ethanolic extract of *C. cancellatus* inhibited the proliferation of MDA-MB-231 and MCF-7 human breast cancer cell lines	t-test SPSS	Shakeri *et al.*, 2022
23.	*Curcuma longa* L. Zingiberaceae	A549 cell line	Lung cancer	UHPLC-HRMS	Curcuminoid	CE (3 cell-binding curcuminoids) and three individual curcuminoid fractions changed the expressions of 25 metabolites in A549 cells, which were involved in glycerophospholipid catabolism, sphingolipid metabolism and fatty acid metabolism	PCA OPLS-DA	Zhou *et al.*, 2019
24.	*Kigelia africana* (Lam) Benth.	Hep G2 cell line, HeLa cell line, A375 cell line, HEK 239 cell line	Hepatic cancer, Melanoma cancer	UHPLC/GC-TOF-MS	Physostigmine Fluazifop Dexamethasone Sulfisomidine Desmethylmirtazapine	Physostigmine is a potent molecule that could be considered a lead compound against topoisomerasi.	PCA Hierarchical Cluster (HCA)	Fagbohun *et al.*, 2020

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
						K. africana fruit extract could be considered an antiproliferative agent of phytochemicals and secondary metabolites		
25.	*Olive tree* leaf extract	JIMT-1 cell line	Breast cancer	HPLC-ESI-Q-TOF-MS	Diosmetin, Apigenin, Luteolin	Diosmetin was the major cellular phenolic metabolite found in SFE. Olive leaf treated JIMT-1 breast cancer cells	ANOVA	Barrajin-Catalan *et al.*, 2015
26.	*Andrographis paniculata*, *Oroxylum indicum, Orthosiphon aristatus, Willughbeia edulis*	Hep-G2 cells	Liver cancer	UHPLC-HRMS	AndrographolactoneDehydroandrographolide, Baicalein, chrysin, oroxylin A, scutellarein, Parabararoside C, procyanidin	Among the four plant species exhibiting the highest anti-proliferative activities on Hep-G2 cells line and well known for the treatment of liver disorder	OPLS	Chassagne *et al.*, 2018
27.	*Plectranthus amboinicus* (Lour.) Spreng	MCF7 cell lines	Breast cancer	HPLC-MS UHPLC-QTOF-MS/MS	Abietane diterpene	The compounds on *P. amboinicus* that contributed to the cytotoxic activity of the plant against MCF7 cells	OPLS	Yulianto *et al.*, 2016
28.	*Xanthium strumarium*	A2780cp cell line	Ovarian cancer	1HNMR	Capric acid, oleic acid, stearic acid,	Metabolic pathways involved in	PLS-DA	R. Malekzade

No.	Specific medicinal plant treatment	Biological Sample	Cancer types	Analytical platform (s)	Biomarkers identified	Main findings	Statistical method	Ref
					propylene glycol, tracylglycerol	cell growth inhibition were limited to tyrosine metabolism, nucleotide metabolism, fatty acid biosynthesis, and glycerolipid metabolism that can be potential therapeutic targets in ovarian cancer		h *et al.*, 2020

This approach uses a tetrazolium salt that can only be cleaved by active mitochondria in metabolically active cells, making it relevant to practically any survival or proliferation assay where living cells must be separated from dead ones.

The MTT method is used to calculate the IC_{50} value (Inhibitory Concentration). The IC50 value is a concentration that generates a 50% cell growth barrier and shows the potential toxicity of a substance to the cell. This number serves as a standard for completing cell kinetic observation experiments and indicates whether a substance is potentially cytostatic. The toxicity is suspected due to the presence of bioactive components such as flavonoids, polyphenols, tannins, and other compounds in medicinal plant extracts that play a role in reducing the number of cancer cells, because reactive oxygen radicals are a compound that plays an important role in the occurrence of carcinogenesis (Amir & Murcitro, 2017).

2. Platform Analysis

Metabolomic is the targeted and non-targeted examination of endogenous and exogenous metabolites (<1500 Da) such as lipids, amino acids, steroids hormone, peptides, nucleic acids, organic acids, vitamins, thiols, and carbohydrates, which represents a promising approach for biomarker development. The complexity of the metabolome, metabolite characteristics, and concentration levels in biological samples hinder separation and detection on a single analytical instrument. In 28 research, many types of analytical platforms were used. As a result of this, the integration of high-resolution analytical frameworks, such as mass spectrometry (MS) and nuclear magnetic resonance (NMR), appears as a result in metabolomics studies, providing sensitive, reliable detection and quantification of thousands of metabolites in a biological sample and related metabolic pathways in a matter of minutes as: study population (BC patients and normal) sample collection data acquisition statistical analysis biological interpretation.

3. Data Processing and Statistical Analysis

The data provided by metabolomics research is complicated and contains a huge number of variables. As a result, the findings of metabolomics investigation are difficult to evaluate using traditional univariate statistical approaches. Multivariate statistical methods are frequently used for the display and interpretation of large amounts of data collected from metabolomics research. PCA (Principal Component Analysis) is a frequent unsupervised method for obtaining a comprehensive perspective of the data. According to Madsen *et al.* (2010), supervised approaches such as PLS-DA (Partial Least Square Discriminant Analysis) and OPLS-DA (Orthogonal Partial Least Square Discriminant Analysis) are used to conduct discriminant analysis and identify biomarkers. Univariate statistical analysis, such as ANOVA was also utilized in some literature in addition to multivariate analysis. Based on Hasanpour *et al.* (2020), these multivariate and univariate statistical methods are often useful in many metabolomics studies.

4. Biomarker and Metabolomic Pathways

The term OMICs refers to a dataset of genomics (DNA), transcriptomics (RNA), proteomics (proteins) and metabolomics (metabolites) based on the fundamental tenet of molecular biology (Moore *et al.*, 2018). The purpose of OMICs science in cancer research is to identify cancer-specific biomarkers (diagnostic, prognostic, and/or putative). Beger (2013) defined a biomarker as a trait that is objectively tested and analyzed as an indicator of normal biological processes or biological responses to a therapeutic intervention. Biomarkers are important tools for early cancer identification and therapeutic strategy selection, which improves cancer treatment outcomes and reduces cancer-related mortality.

Yuan *et al.* (2007) define cancer as dysregulated cell proliferation paired with inhibited programmed cell death. Anticancer drugs that can promote programmed cell death in cancer cells, specifically apoptosis, while limiting undesired effects on surrounding normal cells have gotten a lot of interest because they offer a viable strategy for cancer prevention and treatment. Most chemotherapy medications now used in clinical settings impede cell development and trigger apoptosis. Membrane blebbing, cell shrinkage, chromatin condensation nuclear fragmentation, fragmentation into membrane-bound apoptotic entities, and translocation of membrane PS are some of the usual morphological features that characterize cellular apoptosis (Mukhopadhyay *et al.*, 2014). Cancer development comprises numerous pathways and phases, resulting in faster proliferation than normal cells as well as an increase in glucose metabolism and lactate production (Martinez-Outschoorn *et al.*, 2017).

Most anticancer research has concentrated on the antiproliferative impact of single medications or chemicals through extensive analysis of cell proliferation signaling or metabolic pathways (Corominas-Faja *et al.*, 2012). Several studies have found that bioactive phytocompounds found in plants have an effect on cancer cell proliferation, differentiation and death. Herbal medications and natural products are gaining popularity due to their ability to treat cure chronic diseases such as cancer (Varghese *et al.*, 2020). Herbal medicine can enhance the efficacy of chemotherapy while reducing its side effects and organ toxicity.

According to the findings of 28 research, there are curcumin, flavonoids, betulinic acids, polyphenols, isoquercetin, apigenin and other compounds. Furthermore, medicinal plants and natural product-derived compounds can target cancer cells effectively and selectively without damaging normal cells (Kim *et al.*, 2021). Compounds in medicinal plants have several mechanisms that affect anti-cancer action, such as causing apoptosis, anti-angiogenesis, anti-metastasis, and anti-multidrug resistance (Luo *et al.*, 2016).

CHALLENGES

There are few published data on metabolomics applications to understand the anticancer effects of herbal medications. There have been few studies that translate metabolomics discoveries into clinical applications. Clinical uses of metabolomics in examining the anticancer efficacy of herbal medicine would benefit from a thorough understanding of how metabolite measurements are linked to cancer biology, particularly in easily accessible biofluids. Because of the structural diversity of cancer cells and plant metabolites, absence of specific metabolic signatures for each kind of cancer, and tumor diverse metabolic preferences, metabolite analysis to assess the response of cancer cells to herbal therapies faces numerous difficulties. Other difficulties include separating the anticancer metabolic effects of herbal exposure from general metabolic perturbations in biofluids, the influence of environmental factors, genetic factors, and gut microbiota, sample processing, variance in origin, and cell line handling (Kim *et al.*, 2019). Sample preparation, standardization of instrumentation, high cost of analytical instruments, structurally diverse compounds, data processing and interpretation, availability of trained manpower, and poor publicity of metabolomics compared to other omics technologies are examples of technological limitations specific to metabolomics (Schmidt *et al.*, 2021).

Although there is still much to learn about the metabolic complexity of cancer and the technical aspects of metabolomic profiling, significant progress has been made in the last decade. To present, the majority of cancer metabolomics investigations on medicinal plants have been undertaken using cell lines. While cell lines are useful for studying the metabolic regulatory mechanisms of herbal medicines, systems that can replicate the genetic heterogeneity and microenvironment of human cancers are also required. Significant progress has been achieved in developing metabolome databases and improving metabolite coverage for metabolite identification and data visualization. The discovery of new cancer-type-specific metabolomic signatures and their therapeutic significance will encourage the use of metabolomics studies for cancer medication development from traditional herbal treatments.

CONCLUSION

Metabolomics may help in the detection of potential cancer biomarkers, being useful for example in the development of different devices, including biosensors, that can significantly improve the cancer diagnosis. Also, standard procedures for sample collection, data analysis and shared in repositories have potential to be adopted by both researchers and medical communities. Hopefully, based on our systematic review on the recent mechanism investigation of medicinal plants for cancer therapy from the metabolomic perspective, more attention would be attracted to the clinical application of potential candidates from the resourceful medicinal plants as novel and efficient adjuvant therapeutics for cancer therapy.

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