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Traditional uses, phytochemistry and therapeutic efficacy of cassava (*Manihot esculenta* Crantz) - A Review

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Abstract

The usage of naturally available resources by humans for gratifying different requirements is an age-old custom. This is because natural products provide indispensable facilities in the form of nutritional, economic, social, medicinal aspects and many more. Cassava (*Manihot esculenta* Crantz) has been used as a herbal medicine by different groups of ethnic people. Besides having medicinal prospect, this plant is commonly used as a source of nutrition for humans and animals in tropical regions. However, conduction of more studies are required to see if there is chemical, microbiological, and/or clinical evidence, from a scientific perspective, of their effectiveness for those ailments. Therefore, this review was conducted to summarize the traditional uses, to understand the phytochemistry and identify the possible correlation between bioactive compounds and corresponding pharmacological properties. A systematic and detailed literature search has been undertaken for the study by using standard search engines like Google Scholar, PubMed, SciFinder, Research Gate and Science Direct. The evidential information was then assembled to present the manuscript with separate sections.

From the literature search, it came into focus that Cassava contains various secondary metabolites which exhibits some notable pharmacological activities like antioxidant, antiradical, anticancer, antibacterial, antifungal, antidiarrheal, analgesic and pesticidal activity.

The biological activities established by cassava provide insight into its usage in traditional medicinal systems. But an intricate and thorough review appears to be deficient on *M. esculenta.* Therefore, this review has summarized the studies investigating about the traditional uses, phytochemistry, bioactive compounds and therapeutic efficacy of *M. esculenta*. The significance of this review is aimed at a better understanding of the novel applications and further considerations for more logical and scientific evaluation. We hope this study will further aid in the development of research on this area to identify a new generation of natural source-based treatments that will help meet the growing consumer demand for safe, sustainable, and natural treatments.

Keywords

flavonoids; *Manihot esculenta*; pharmacological activities; phenols; phytochemistry; traditional uses

Introduction

Manihot esculenta Crantz is an edible dicotyledonous perennial plant belonging to the family Euphorbiaceae (2). It is a semi-woody shrub that originated in South America. *M. esculenta* is commonly known as cassava, tapioca, sweet potato tree, Brazilian arrowroot and by different local names in different parts of the world (Fig. 1). It is being widely cultivated in tropical and subtropical regions of the world as it acts as a reservoir of carbohydrates

Fig 1. The plant *Manihot esculenta* in its natural habitat

in tropical regions. Cassava leaf is a native edible vegetable and it is also a potential alternate source of protein for both humans as well as animals (3). Cassava leaves are an enormous source of proteins, carbohydrates, vitamins and minerals (4, 5). Besides having nutritional value, *M. esculenta* is an integral part of folk medicinal practice. It is used for treatment of different health conditions indigenously (6).

Apart from having medicinal properties, Cassava is also consumed as staple food by people in Ghana, Africa as it serves as source of stored carbohydrates in its roots, leaves and tubers. Cassava besides being an important part of diet amongst African population also has economic importance as almost half of the world's cassava estimating nearly 86 million tons is produced in Africa (7). Therefore, this review aims to make a proper and systematic documentation of the indigenous uses, phytochemistry, identified active components, pharmacological efficacy of *Manihot esculenta* as these will provide a new perspective in future novel investigations for drug development.

A systematic literature search was performed using scientific databases such as PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/), SciFinder, Research Gate (https://www.researchgate.net/), Science Direct. The search terminologies like "indigenous uses of cassava", "secondary metabolites present in cassava", "isolated compounds from *Manihot esculenta*", biological activities reported in *Manihot esculenta*" were used for critical analysis of the works being done earlier. A total of 52 articles were found to be relevant to the area of interest. The published works having constructive and useful information relevant to the review was selected and the manuscript was summarized with separate sections assembling all the applicable data. Based upon the analyses of data obtained from selected articles, we formulated several important findings which are a summary shown in tables.

1. Morphology of the plant

Manihot esculenta is a shrub having yellowish grey smooth bark. It grows upto an average height of 4m. Leaves are dark green above and pale yellowish below and show an alternate arrangement. The inflorescence is lax with 3 to 5 together in fascicles. Male flowers are greenish-white in appearance with reddish-white bands inside. The anthers are yellow and disc is yellow to light orange in appearance. Female flowers are perianth green with red margin and midrib and the ovary contains 6 longitudinal ridges (1).

2. Distribution

The plant is native to Brazil and now is found throughout tropical regions. In India, it is found in Maharashtra, Karnataka, Kerala, Tamil Nadu and in North Eastern India particularly in Assam, Meghalaya (1).

3. Traditional uses of *Manihot esculenta*

Manihot esculenta is traditionally consumed as a primary green vegetable in different countries like Latin America, Philippines, Indonesia, Malaysia and some other Asian countries (8, 9). It is an important part of the Nigerian traditional medicinal system. The leaves and seeds of *M. esculenta* are being used to treat different types of ailments traditionally to meet up with health challenges from ancient times (Table 1). The leaves and seeds are traditionally used for curing fever, headache, rheumatism, and hemorrhoids (6). In Nigerian folk practice, *M. esculenta* is utilized as a remedy for ringworms, tumor, conjunctivitis, sores and lesions (6). Some literature citation has also reported the therapeutic use of *M. esculenta* leaves in hypertension, aches, irritable bowel syndrome, cancerous affections and dysentery. The leaves are also employed as an effective remedial agent in flu, marasmus, snake bites, prostatitis, spasms, and as an antiseptic, diuretic, cyanogenetic and demulcent herbal agent (10-12) (Table 1).

4. Phytochemistry of *Manihot esculenta*

The pharmacological activity of medicinal plants is mainly contributed by secondary metabolites present in them. These secondary metabolites are of different classes namely alkaloids, glycosides, flavonoids, tannins, terpenoids, proanthocyanidins, furocoumarins, naphthodianthrones, proteins, and peptides (13). The leaves of *Manihot esculenta* has been reported to contain alkaloids, flavonoids, phenols, tannins, terpenoids, anthraquinones, phlobatannins, saponins, reducing sugars, anthrocyanosides. The presence of cyanogenic glycosides such as lotaustralin and linmarin, noncyanogenic glycosides, hydroxycoumarins has been reported in the fresh leaves of Cassava and in its roots (14-17). Besides this, the plant is also rich in different types of macro and micronutrients and contains antioxidants like â-carotene, vitamins like vitamin A and C (3, 18, 19) (Table 2).

5. Bioactive compounds identified and isolated from *Manihot esculenta*

A previous study conducted by Yi and his coworkers (2010) identified and isolated ten antioxidant compounds for the first time from the stem of Cassava namely coniferaldehyde, isovanillin, 6-deoxyjacareubin, scopoletin, syringaldehyde, pinoresinol, p-coumaric acid, ficusol, balanophonin and ethamivan (20) (Fig. 2). Another research conducted has reported phenolic compound in leaves namely coumarin, scopolin, scopoletin, aglycone and flavonoids namely Kaempferol-3-O-rutinoside and rutin (21) (Table 2).

Table 1. Traditional uses of different parts of *Manihot esculenta*

Sl No.	Region	Plant part used	Mode of application	Pharmacological action	References
1	Indonesia, Malaysia	Leaves	Decoction	Fever	(6), (10)
2	Indonesia, Malaysia	Leaves	Decoction	Headache	(6), (10)
3	Indonesia	Leaves	Hot water extract	Rheumatism	(6)
4	Indonesia	Seeds	Infusion (Herbal pill)	Hemorrhoids	(6)
5	Nigeria	Leaves	Powder, paste, Decoction	Ringworms	(6)
6	Nigeria	Leaves	Decoction	Tumor	(6), (11)
7	Nigeria	Leaves	Paste, hot water extract	Conjunctivitis	(6)
8	Nigeria	Leaves	Powder	Sores and lesions	(6)
9	Malaysia	Leaves	Leaf paste	Hypertension	(10)
10	Malaysia	Leaves	-	Aches	(10)
11	Nigeria	Leaves	Decoction	Irritable bowel syndrome	(10)
12	Nigeria	Leaves	Decoction	Cancerous affections	(11)
13	Nigeria	Leaves, roots	Decoction	Outgrowth of eye and tumor	(11)
14	Nigeria	Leaves	Decoction	Dysentery	(10)
15	Nigeria	Leaves	Decoction	Flu	(11), (12)
16	Nigeria	Leaves	Paste	Marasmus	(11), (12)
17	Nigeria	Leaves	Paste	Snake bites	(12)
18	Nigeria	Leaves	Decoction	Prostatitis	(12)
19	Nigeria	Leaves	Decoction	Spasms	(12)
20	Nigeria	Leaves	Decoction	Antiseptic	(12)
21	Nigeria	Leaves	Decoction	Diuretic	(12)
22	Nigeria	Leaves	Decoction	Cyanogenetic	(12)
23	Nigeria	Leaves	Decoction	Demulcent	(12)

Source: Self compiled from different published works as cited.

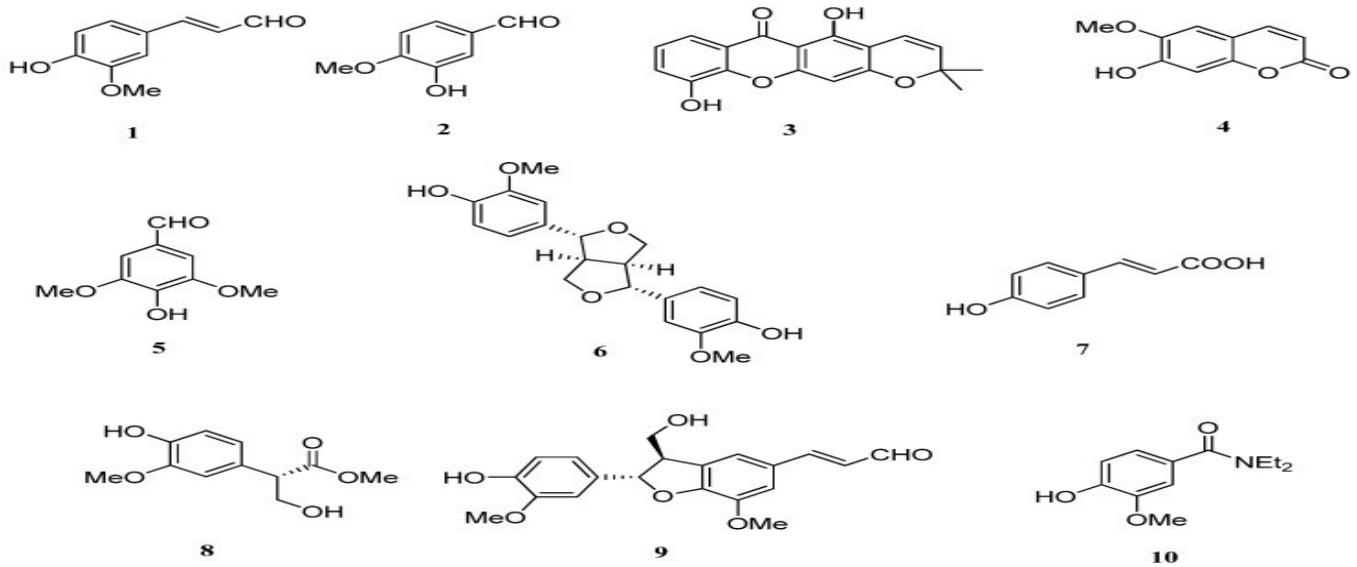

Fig.2. Chemical structure of bioactive compounds isolated from *Manihot esculenta (*1- Coniferaldehyde, 2- isovanillin, 3- 6-deoxyjacareubin, 4- scopoletin, 5- syringaldehyde, 6- pinoresinol, 7- p-coumaric acid, 8- ficusol, 9- balanophonin, 10- ethamivan) (Yi et al., 2010).

Source: Self compiled from different published works as cited.

Table 2. Phytochemistry and Bioactive compounds isolated from *Manihot esculenta*

Sl. No.	Type of compound	Name of the compound	Plant part from where extracted/identified/ documented	Process of detection/ isolation/extraction	Reference
1	Alkaloids		Tubers and leaves	-	14
2	Glycosides	Lotaustralin	Aerial parts, roots	HPLC	15,17
		Linmarin	Aerial parts, roots	HPLC	15, 17
		Hydroxycoumarins	Roots	-	15
3		Ethyl β-D-glucopyranoside	Root cortex	-	16
4		Kaempferol-3-O-rutinoside	Tubers and leaves	HPLC	16, 21
	Flavonoids	Rutin	Tubers and leaves	HPLC	16
		Quercetin-3-*O*-rutinoside	Leaves	-	16
		Gallocatechin	Roots	HPLC	17
5	Phenols	Coumarin	Leaves	HPLC	21
		Coumarin	Root	HPLC	17
		Aglycone	Leaves	-	21
		Scopoletin	Leaves	HPLC	15, 21
		Scopoletin	Roots	HPLC	17
		Scopolin	Roots	-	15
		Scopolin	Leaves	-	21
		Coniferaldehyde	Stem	Column chromatography	20
		Scopoletin	Stem	Column chromatography	20
		Isovanillin	Stem	Column chromatography	20
		6-Deoxyjacareubin	Stem	Column chromatography	20
		Pinoresinol	Stem	Column chromatography	20
		p-Coumaric acid	Stem	Column chromatography	20
		Ficusol	Stem	Column chromatography	20
		Balanophonin	Stem	Column chromatography	20
		Ethamivan	Stem	Column chromatography	20
6	Carotenoids	â-carotene	Leaves	Ultraviolet spectrophotometry	3,18,19
7	Vitamins	vitamin A	Tubers and leaves		14
		vitamin C	Tubers and leaves		14
		Vitamin E	Tubers and leaves		14

Source: Self compiled from different published works as cited.

6. Pharmacological activity

As per the literature survey, different parts of *Manihot esculenta* have some significant pharmacological activities like antioxidant, antiradical, anticancer, antibacterial, antifungal, antidiarrheal and analgesic while extracted with different solvents (Table 3).

6.1 Antioxidant activity

A study was carried out to analyze antioxidants present in Indian Cassava. The study focused on the extraction of total phenolic content, anthocyanins and other flavonoids. Three different solvents (acidified methanol, methanol and acetone) were used for the extraction of total phenol and anthocyanins. The acidified methanolic extract yielded the highest quantity of anthocyanin whereas acetone extract yielded the highest total phenol contents. The antioxidant assays carried out demonstrated that all the extracts have emerged as good scavengers of free radicals contributed by H^+ion (22). In a similar study, it was reported that the aqueous leaf extract of *Manihot esculenta* has markedly decreased the production of lipid hydroperoxides in a dose-dependent manner. The extract sufficiently minimized the formation of volatile markers of lipid peroxidation such as ethylene which was measured using gas chromatography. Furthermore, the use of the Fluorescence technique revealed that the extract reduced the cellular production of ROS by activating monocytes in HL-60 cells (23). Additionally, the ethanolic leaf extract of *M. esculenta* exhibited mild DPPH scavenging activity and significant superoxide activity against NBT. The extract also showed moderate xanthine oxidase inhibition activity and very low pancreatic lipase inhibitory potential (24).

6.2 Antiradical activity

The aqueous leaf extract of *Manihot esculenta* showed a remarkable antiradical activity**.** The extract demonstrated inhibitory effects about 55% and 49% in non-heated and boiled sample respectively. In comparison to aqueous extract of *Pteridium aquilinum*, *Abelmoschus esculentus*, *Hibiscus acetosella, M. esculenta* has shown a maximum inhibitory efficiency in a concentration dependent manner without much significant difference. The production of intermediate peroxyl and different free radicals by different extracts in the study was measured by ESR technique using POBN as a spin trap agent (23).

6.3 Anticancer activity

The anticancer activity of crude methanolic and aqueous callus extracts of *Manihot esculenta* against breast carcinoma cell lines (MCF7) was also evaluated. Agarose gel electrophoresis and flowcytometry was used to assess the DNA damage intoxicated in breast cancer cell line. The result showed that the methanolic and aqueous callus extract of *M. esculenta* had demonstrated cytotoxic activity at the dose of 0, 2.5, 5, 10, 20 µg/mL by inhibiting the growth of treated breast carcinoma cells as compared to the untreated cells. During the study, IC_{50}values for methanolic and aqueous extract were found to be 1.43 and 1.3 respectively (25).

Table 3. Pharmacological Activities of different extracts of *Manihot esculenta*

Plant part	Solvent used	Assay	Pharmacological actions	References
Leaf stalk	Acidified methanol Methanol Acetone	*In vitro*	The acidified methanolic extract yielded highest quantity of anthocyanin whereas acetone extract yielded highest total phenol contents	(22)
Leaves	Aqueous	*In vitro*	The aqueous leaf extract of *Manihot esculenta* has markedly decreased the production of lipid hydroperoxides in a dose dependent manner	(23)
Leaves	Ethanol	*In vitro*	The ethanolic leaf extract of *M. esculenta* exhibited mild DPPH scavenging activity and significant superoxide activity against NBT.	(24)
Leaves	Aqueous	*In vitro*	In comparison to aqueous extract of *Pteridium aquilinum*, *Abelmoschus esculentus*, *Hibiscus acetosella, M. esculenta* have showed a maximum inhibitory efficiency in a concentration dependent manner without much significant difference	(23)
Stem	Aqueous Methanol	*In vitro*	The result showed that the methanolic and aqueous callus extract of *M. esculenta* had demonstrated cytotoxic activity at the dose of 0, 2.5,5, 10,20 µg/ml by inhibiting the growth of treated breast carcinoma cells as compared to the untreated cells.	(25)
Leaves	Ethanol	*In vitro*	The extract showed maximum zone of inhibition of 8.1mm against *Pseudomonas aeruginosa* at the concentration of 250 mg/ml and no inhibition zone was shown by the extract at any concentration (5, 50, 100, 250 mg/ml) against *E. coli*	(26)
Leaves	Methanol	*In vitro*	The methanolic extract of cassava leaf showed maximum activity against *Staphylococcus aureus* by forming a zone of inhibition of 16mm while least activity was reported in the acetone extract against *Pseudomonas aeruginosa* (2.5 mm)	(27)
Leaves	Hydroethanol	*In vitro*	Hydroethanolic extract of *M. esculenta* showed the effect only on *P. aeruginosa* meropenem resistant at the concentration of 500 µg/ml whereas it failed to show any effect against *S. aureus*	(33)
Leaves	Aqueous	*In vitro*	*M. esculenta* showed 60.2% in inhibition *A. niger* and 68.2% against *B. theobromae* at the concentration of 75g/L after 144 hrs of incubation	(27)
Leaves	Ethanol	*In vivo*	The extract showed antidiarrheal activity by inhibiting the intestinal fluid by 44.44% at the dose of 200 mg/kg body weight, 22.22 % inhibition at the dose of 100 mg/ kg body weight whereas a statistically insignificant inhibitory activity of 5.55% was demonstrated at the dose of 50mg/kg body weight	(28)
Leaves	Ethanol	*In vivo*	The extract showed lesser analgesic activity of 62.14% at dosage of 51.3 mg/kg body weight and 55.9% at higher dose of 102.6 mg/kg body weight	(6)
Leaves	Petroleum ether, Ethanol Ethyl acetate	*In vivo*	The ethyl acetate extract showed higher pesticidal activity of 95% at high dose after 48 hr and 97% at the same dose after 72 hr than ethanol and petroleum ether extracts	(29)

Source: Self-compiled from different published works as cited.

6.4 Antibacterial activity

The ethanolic leaf extract of *Manihot esculenta* reported antibacterial activity against specific bacterial strains such as *E. coli* (T. Escherich, 1885-Enterobacteriaceae), *Klebsiella pneumoniae* (Schroeter, 1886-Enterobacteriaceae), *Pseudomonas aeruginosa* (Schroeter, 1872-Pseudomonadaceae), *Staphylococcus aureus* (Rosenbach, 1884-Staphylococcaceae) *and Bacillus subtilis* (Ehrenberg, 1835-Bacillaceae). The extract showed maximum zone of inhibition of 8.1mm against *Pseudomonas aeruginosa* at the concentration of 250 mg/ml and no inhibition zone was shown by the extract at any concentration (5, 50, 100, 250 mg/ml) against *E. coli* (26). In a similar finding, it was observed that the methanolic extract of Cassava leaf showed maximum activity against *Staphylococcus aureus* by forming a zone of inhibition of 16 mm while the least activity was reported in the acetone extract against *Pseudomonas aeruginosa* (2.5 mm) (27). Another work on hydroethanolic extract of *M. esculenta* showed the effect only on *P. aeruginosa* meropenem resistant at the concentration of 500 µg/mL whereas it failed to show any effect against *S. aureus* (33).

6.5 Antifungal activity

The antifungal efficacy of *M. esculenta* was investigated against pathogenic fungi *Aspergillus niger* (Van Tieghem, 1835-Trichocomaceae) and *Botryodiplodia theobromae* (Patouillard and Lagerheim, 1892- Botryosphaeriaceae). The fungi were isolated from worn out tubers of yam using antibiotic amended Potato Dextrose Agar. Different concentrations of the extract (25g/L, 50g/L and 75g/L) and Camazeb (5g/L, 10g/L) were used against each fungus on PDA plates. The leaf extract of *M. esculenta* demonstrated very little inhibitory effect against both the phytopathogens in comparison to *Colocasia esculenta* and *Dioscorea rotundata*. *M. esculenta* showed significant 60.2% against *A. niger* and 68.2% against *B. theobromae* at the concentration of 75g/L after 144 hr of incubation (27).

6.6 Antidiarrheal activity

A study reported the antidiarrheal activity of ethanolic leaf extract of *Manihot esculenta* in Wistar rats. The rats were treated with three different doses of *M. esculenta* leaf extract (50 mg/kg body weight, 100 mg/kg body weight and 200 mg/kg body weight). Charcoal passage test and castor oil-induced fluid accumulation method were used for examining the antidiarrheal efficacy. The extract showed antidiarrheal activity by inhibiting the intestinal fluid by 44.44% at the dose of 200 mg/kg body weight, 22.22 % inhibition at the dose of 100 mg/kg body weight whereas a statistically insignificant inhibitory activity of 5.55% was demonstrated at the dose of 50 mg/kg body weight (28).

6.7 Analgesic activity

The ethanolic leaf extract of *Manihot esculenta* at different doses (12.8 mg/kg body weight, 25.6 mg/kg body weight, 51.3 mg/kg body weight, 102.6 mg/kg body weight) showed a reduction of pain in mice that was induced by 0.6% acetic acid. The analgesic power was highest at 25.6 mg/kg body weight concentration showing a 73.94% increase in writhing protection. Surprisingly, the extract showed lesser analgesic activity of 62.14% at a dosage of 51.3 mg/kg body weight and 55.9% at a higher dose of 102.6 mg/kg body weight (6).

6.8 Pesticidal activity

The leaf extract of *Manihot esculenta* was found to be highly toxic against the red flour beetle (*Tribolium castaneum*) which is a worldwide pest of stored food grains. Extracts were prepared in three different solvents (petroleum ether, ethanol and ethyl acetate) and were tested for pesticidal activity at different concentrations (150 ppm, 300 ppm, 500 ppm) at three-time intervals (24 hr, 48 hr, 72 hr). All three extracts have shown promising mortality rate of pests in a dose and time dependent manner. After 24 hr, ethyl acetate showed highest mortality (82%, 89% and 93% at 150, 300 and 500 ppm) and petroleum ether extract showed lesser mortality (50%, 70% and 83% at 150, 300 and 500 ppm). Whereas ethanol extract showed medium mortality (62%, 78%, 87% at 150, 300 and 500 ppm). The ethyl acetate extract showed higher pesticidal activity of 95% at a high dose after 48 hr and 97% at the same dose after 72 hr than ethanol and petroleum ether extracts (29).

The existing literature related to *Manihot esculenta* showed that they involve studies on a particular biological property or its effect against a particular disease. But a precise and in-depth review of the indigenous uses, phytocompounds present and their relationship with pharmacological efficacies is not done. This study has tried to address all the prospects with a special focus on scientifically validated uses, screened and isolated metabolites and therapeutic properties. From the literature study, it is well understood that different parts of the plant have folklore uses and many of them are evidentially proved. *M. esculenta* has testified phytochemicals like alkaloids, flavonoids, phenols, tannins, terpenoids, anthraquinones, phlobatannins, saponins, reducing sugars and anthrocyanosides in different solvents. Most of the phytocompounds present in the plant are identified from *M. esculenta* stem (coniferaldehyde, isovanillin, 6-deoxyjacareubin, scopoletin, syringaldehyde, pinoresinol, p-coumaric acid, ficusol, balanophonin, ethamivan), *M. esculenta* leaves (coumarin, scopolin, scopoletin, aglycone and flavonoids namely Kaempferol-3-O-rutinoside and rutin) (20). The plant has displayed a spectrum of medicinal benefits including antioxidant, antiradical, anticancer, antibacterial, antifungal, antidiarrheal, pesticidal and analgesic.

Conclusion

The findings specify that plants are endowed with useful properties that can be harnessed inexpensively. Nowadays, plant-based products are in higher demand because of the fact that synthetically derived products possess the capacity to luster a harmful impact on humans as well as on the entire ecosystem. This review indicates that *Manihot esculenta* is a less acknowledged medicinal plant having enormous nutritional as well as pharmaceutical properties. All the researches have scientifically manifested the use of the plant in folk medicinal practice in different parts of the world. However, there are still many traditional uses of this plant which needs detailed scientific finding so that a clear and genuine validation of the uses is established. Moreover, the bioactive compounds isolated from the plant also require an elaborative pharmacological screening for their potent biological properties. There is also a lack of information on the safety aspect of the plant which urges for performing toxicological studies on extracts, and isolated secondary metabolites from *M. esculenta.*

Authors' contributions

BS shaped and wrote the manuscript. TS and KD summarized the manuscript and MKB conceived and analyzed the data.

Compliance with ethical standards

Conflict of interest: There is no conflict of interest.

Ethical issues: None.

Abbreviations:

ROS- Reactive Oxygen Species

HL-60- Human Leukemia cell line-60

DPPH- 2,2-diphenyl-1-picrylhydrazyl

NBT- Nitroblue Tetrazolium

ESR- Electron Spin Resonance

POBN- α-(4-pyridyl-1-oxide)-*N*-*tert*-butylnitrone

MCF7- Michigan Cancer Foundation-7

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