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ESTIMATION OF SECONDARY METABOLITES AND TOXICITY TO *ARTEMIA SALINA* L. OF SELECTED PLANTS OF FAMILY COMBRETACEAE: AN APPROACH FOR SCREENING OF HERBAL PREVENTIVE AGENTS

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ABSTRACT: Objective: Combretaceae, a large family, includes more valuable species that are used against many diseases and disorders along with cancer therapy. Cancer is a very common lethal disease throughout the world. Keeping this in view, two species are *Combretum roxburghii* Spreng and *Terminalia catappa* L. selected for present studies to provide baseline data for future formulation. **Methods:** Phytochemicals were detected in different extracts of experimental plants. The cytotoxicity was tested using a Brine shrimp assay. The presence of both total phenol and total tannin content was estimated by standard spectrophotometric methods. **Results:** *Terminalia catappa* L. showed the presence of a number of natural bioactive compounds than *Combretum roxburghii* Spreng. The lethality test indicated maximum in *Combretum roxburghii* Spreng. (leaf) in methanol extract and *Terminalia catappa* L. in acetone extract (leaf). The highest concentration of total phenol and tannin content was observed in *Combretum roxburghii* Spreng. Conclusion: Phytochemical test, cytotoxicity test, total phenol & tannin content indicated the pharmacological potential and preventive characters against cancer and formulation of future drugs.

INTRODUCTION: According to World Health Organisation, 80 % of the world's people depend upon traditional medicines for their primary health care issues [1]. Traditional knowledge and the use of local plants.

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For primary needs remain important, not only in rural or tribal areas but even in urban and semi-urban areas.

Traditional medicine combines both knowledge and practices, whether explainable or not; it is used in disease diagnosis and treatment, prevention and elimination of physical, mental, or social imbalance and relies exclusively on practical experience and observations that are transferred from generation to generation by individuals [2]. Today, there is an increasing desire to reveal the role of ethnobotanical knowledge by capturing centuries-

old traditional folk knowledge from elderly people as well as by searching for new plant species of medicinal and economic importance [3]. The medicinal potential of plant species and parts that are used for the preparation and administration of various drugs vary with climate and environmental conditions [4]. However, the knowledge of herbal medicine is gradually dying out, although some traditional herbal healers around the world continue to practice the art of herbal healing effectively [5]. These traditional medicines are isolated from different plants, plant parts, and plant products. About 25-50% of pharmaceuticals and drugs are isolated from plants or different plant parts [6].

TABLE 1: PHARMACOLOGICAL ACTIVITIES OF DIFFERENT PLANTS OF COMBRETACEAE FAMILY

S. no.	Scientific name	Parts used	Secondary compounds	Uses	References
1.	*Terminalia citrina (Gaertn.) Roxb. ex Flem.*	Leaves	Alkaloid, Saponin & Anthraquinone	Anthelmenthic	19
2.	*Terminalia avicennioides Guill & Perr.*	Stem bark & root	Phenol, elagic acid & sterol	Antimicrobial activity	20
3.	*Combretum krausii* Hochst.	Leaves	Alkaloid, steroid & cardiac glycosides	Antimicrobial activity	21
4.	*Combretum collinum Fresen.*	Fruit & leave	Flavonoid & steroid	Antimicrobial activity	22
5.	*Terminalia ivorensis A. Chev.*	Trunk	Flavonoid, sterol, coumarin & terpenoid	Antibacterial activity	23
6.	*Conocarpus erectus* L.	Fruit & stem	Phenol & flavonoid	Antioxidant activities	24
7.	*Combretum quadrangulare* Kurz	Leaf & seed	Tannin, terpenoid & sterol	Cytotoxic & hepatoprotective activities	25
8.	*Terminalia arjuna (Roxb.) Wight & Arn.*	Leaf & stem	Phytosterol, flavonoid & phenolic compound	Antioxidant activities	26
9.	*Terminalia schimperina Hochst. ex Engl. & Diels*	Root & bark	Stigmasterol	Antioxidant	27
10.	*Combretum erythrophyllum(Burch.) Sond.*	Stem & bark	Flavonoid & saponin	Antifungal & anti-inflammation	28
11.	*Terminalia macroptera Guill. & Perr.*	Stem & bark	Sterol, terpenoid & cardiac glycosides	Antibacterial activities	29
12.	*Combretum apiculatum Sond.*	Leaves	Cardomamin & pinoembrin	Antibacterial, antioxidant & anti-inflammatory	30
13.	*Terminalia bellarica (Gaertn.) Roxb.*	Leaves, stem & fruit pulp	Phenolic compounds	Antibacterial activities	31
14.	*Combretum glutinosumPerr. ex DC.*	Leaves	Tannin, saponin & flavonoid	Antisickling activity	32
15.	*Terminalia alata* Heyne *ex* Roth	Stem	Steroid & terpenoid,	Antimicrobial activity	33
16.	*Terminalia arjun (Roxb.) Wight & Arn.a*	Bark	Flavonoid	Antiatherogenic activities	34
17.	*Combretum nelsonii Duemmer*	Leaf	Triterpene	Antifungal	35
18.	*Combretum tanaense* J.Clark	Root	L- ascorbic acid, phenol, saponin & glycosides	Antioxidant activities	36

In recent years, it has been observed that some of the important plant species are extinct rapidly due to anthropogenic activities. Medicinal plants produce a high amount of phytochemicals with little or no toxic effect that can be used as antimicrobial or antioxidant activities or development of new drugs [7]. Approximately 250000-500000 plant species have been used for medicinal purposes, and 75 % of anticancer agents are isolated from plant sources. Cancer is a leading cause of death worldwide, and it is rising rapidly from day to day. In 2007, cancer caused 13% of death worldwide [8]. A normal cell undergoes regulated division, differentiation, and apoptosis. Carcinogenesis is the process Characterised by when a normal cell has lost unusual control over

the division differentiation and apoptosis to become a cancer cell. These cells are called cancer cells, tumour cell or malignant cell. These abnormal cells have potential to spread or invade the surroundings and distant tissues. According to epidemiological studies, the incidence of most cancer increases exponentially with age [9]. Some plants of the plant kingdom contain a wide variety of free radical scavenging molecules and some endogenous metabolites, and these molecules possess antioxidant activities and act as preventive as well as curative agents. The family Combretaceae is a major group of flowering plants (Angiosperms) included under the order of Myrtales, and among them, Combretum, Terminalia, and Quisqualis are the largest genera of Combretaceae [10]. Many researchers have reported **Table 1**. the anti-cancer activity & other pharmacological values of plants belong to the family Combretaceae [11, 18]. Keeping the burning problems, two plants (*Terminalia catappa* L. and *Combretum roxburghii* Spreng.) were selected for the present works.

MATERIALS AND METHODS:

Collection and Preparation of Plant Material: The leaves of *Terminalia catappa* L. and *Combretum roxburghii* Spreng. were collected from different locations of Khordha district of Odisha. Then the leaf of these plants was washed thoroughly by tap water and then dried at room temperature. The dried leaves were cut into small pieces with a knife. The dried leaves were powered by using mechanical devices. Then the powdered leaf material was kept in an air-tight plastic container for experimental works [37].

Preparation of Crude Extract: 25 g of powered leaf was taken in a thimble, and the thimble was placed in the Soxhlet apparatus. Methanol (250 ml), Acetone (250 ml) and Distilled water (250 ml) were taken as a solvent for extraction three times of each plant. Then the solvent was removed and the crude extract was extracted from the solvent by reduction of temperature. Finally, the crude extract was produced and stored in the refrigerator for further use [38].

Phytochemical Assays: Phytochemical analysis was carried out on different leaf extracts by using the standard procedure to identify the presence of bioactive compounds [39].

Brine Shrimp Test: For brine shrimp lethality assay [40] (BSLA), the crude extract was prepared by using distilled water, methanol, and acetone. 25 g of plant extract was dissolved in 250 ml of distilled water, acetone and methanol. After few hours the material was filtrated and concentrated on getting some solid mass. Then the shrimp eggs were kept for hatching in saline water for 18 h. Plant extract obtaining following the above protocol was subjected to motility assay.

The 5% DMSO (Dimethyl sulfoxide) was taken as a standard solvent for dissolving extract and is suitable for brine shrimp assay. The toxicity of leaf extract in distilled water, methanol, and acetone was done using brine shrimp assay and noted the maximum inhibition point in different chemicals. Readings were taken up to 4 h and later at 24 h. Motility parameters such as +4 indicate high motile, +3 indicate motile, +2 indicate sluggishly, and +1 indicate slowly. This maximum inhibition point indicates that the leaf might be used as anticancer agents.

Quantification of Anti-Nutritional Factors and Secondary Metabolites [41]:

Extraction of Phenol: 0.5 g of plant extract was taken and crushed with 60 % methanol in mortar and pestle. Sample was centrifuged 5 times at 5000 rpm for 20 min.

Estimation of Phenol: Seven test tubes were taken, including blank and two test tubes for each replica. 0.1 and 0.2 ml of sample was taken in each test tube except blank. 60% methanol was added to each test tube to make volume up to 1 ml. 1 mL of 0.1 NHCL was added and allowed to stand for a few min. 1 mL of sodium nitrite molybdate mixture was added, shaken well, and allowed to stand for few minutes, diluted with 5 mL of distilled water. After dilution, 2 ml of 1N NaOH was added and allowed to stand for 20 minutes. Readings were taken at 515 nm. The amount of phenol present in the sample was calculated from the standard graph.

Estimation of Tannin: 0.5 mg of tanic acid was mixed with 1 ml of distilled water, and from this solution 5, 15, 25, 35, 50 µL were taken in different test tubes. The volume was maintained up to 1 ml. The 0.5 mL of folin reagents and 2.5 ml of 20% sodium carbonate were added to each test tube.

Then mixed solutions were shaking for 5 min in dark conditions. Then the solution of each test tube was left for 40 min. After 40 min reading was taken at 720 nm.

Extraction of Tannin: 0.5 mg of sample was transferred into a 250 ml of the conical flask to which 75 ml of distilled water was added and boiled for 30 min. The whole solution was centrifuged at 2000 rpm for min. The supernatant was taken in a 100 ml volumetric flask, and 75 mL of distilled water, 5 ml of Folin reagent, and 10 ml of 20 % sodium carbonate were added. The volume was made up to 100 m. After shaking 5 min, the reading was taken at 720 nm. The amount of tannin was calculated from the standard graph.

Results and Discussion: The qualitative analysis of experimental plant extracts showed tannin, saponin, phenolic compounds, steroid, and terpenoids **Table 2.** The results revealed that plants possess preventive secondary metabolites against cancer & other researchers have also reported the bioactive compounds [42, 43]. Therefore, cytotoxicity tests have been carried out against *Artemia salina.*

TABLE 2: PHYTOCHEMICAL SCREENING OF EXPERIMENTAL PLANT SPECIES

Plants	Extract	Secondary metabolites detected
C. roxburghii Spreng.	Aqueous	Saponin, Tannin, Steroid, Phenolic compounds
	Ethanol	Saponin, Tannin, Phenolic compounds
	Methanol	Saponin, Terpenoid, Tannin, Steroid, Phenolic compounds
	Acetone	Saponin, Terpenoid, Tannin, Steroid, Phenolic compounds
T. catappa L.	Aqueous	Saponin, Tannin, Phenolic compounds
	Ethanol	Saponin, Terpenoid, Steroid, Phenolic compounds
	Methanol	Saponin, Terpenoid, Steroid, Phenolic compounds
	Acetone	Saponin, Terpenoid, Steroid, Phenolic compounds

Brine Shrimp Lethality Test: The aqueous extract showed a very weak inhibition effect for brine shrimp. All the brine shrimps survived at different concentrations except 500 g/ml. This extract had a very little cytotoxic effect on brine shrimp at a concentration of 500 g/ml. Their % of lethality was 80 % in 500 g/ml **Table 3**.

TABLE 3: TOXICITY TEST OF *T. CATAPPA* L. (AQUEOUS EXTRACT)

Sample		Time									% of Inhibition
		10 min	20 min	30 min	60 min	2h	3h	4h	18 h	24 h	
Aqueous extract	500 g/ml	+4	+4	+4	+4	+4	4+	+4	+4	+2	80
	400 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	+4	0
	300 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	+4	0
	200 g/ml	+4	+4	+4	4+4	+4	+4	+4	4+4	++4	0
	100 g/ml	+4	+4	+4	+4	+4	4+4	+4	+4	+4	0
Distilled water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Brine water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
5% DMSO		+4	+4	+4	+4+	+4	+4	+4	+4	+4	0

TABLE 4: TOXICITY TEST OF *T. CATAPPA* L. METHANOL EXTRACT

Sample		Time									% of Inhibition
		10 min	20 min	30 min	60 min	2 h	3 h	4 h	18 h	24 h	
Methanol extract	500 g/ml	+4	+4	+4	+4	+4	+4	+4	0	0	100
	400 g/ml	+4	+4	+4	+4	+4	+4	+4	0	0	100
	300 g/ml	+4	+4	+4	+4	+4	+4	+4	6	2	80
	200 g/ml	+4	+4	+4	+4	+4	+4	+4	6	1	90
	100 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Distilled water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Brine water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
5% DMSO		+4	+4	+4	+4	+4	+4	+4	+4	+4	0

The methanolic extract of *T. catappa* L. showed a cytotoxic effect on the brine shrimp. All brine shrimp survived in distilled water, brine water, 5% DMSO, and 100 g/ml. Some of the brine shrimp

dead in the concentration of 300 g/ml, 200 g/ml, and all dead in 400 g/ml and 500 g/ml. The % of lethality of brine shrimp was 100% in 500 g/ml, 400 g/ml, 80% in 300 g/ml and 90% in 200 g/ml **Table 4.**The acetone extract of *Terminalia catappa* L. indicated the presence of all survived brine shrimp in distilled water, brine water, and 5% DMSO **Fig. 1.** Some of the brine shrimp dead in 100 g/ml, 200 g/ml and dead in 300 g/ml, 400 g/ml, 500 g/ml. Their % of lethality were 100% in 500 g/ml, 400 g/ml, 300 g/ml, 90% in 200 g/ml and 100 g/ml **Table 5.**

TABLE 5: TOXICITY TEST OF *T. CATAPPA* L. (ACETONE EXTRACT)

Sample		Time									% of Inhibition
		10 min	20 min	30 min	60 min	2 h	3 hr	4 h	18 h	24 h	
Acetone extract	500 g/ml	+4	+3	+2	+1	+1	+1	+1	0	0	100
	400 g/ml	+4	+4	+3	+2	+2	+2	+2	0	0	100
	300 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	0	100
	200 g/ml	+4	+4	+4	+4	+4	+4	+4	+1	+1	90
	100 g/ml	+4	+4	+4	+4	+4	+4	+4	+3	+2	80
Distilled water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Brine water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
5 % DMSO		+4	+4	+4	+4	+4	+4	+4	+4	+4	0

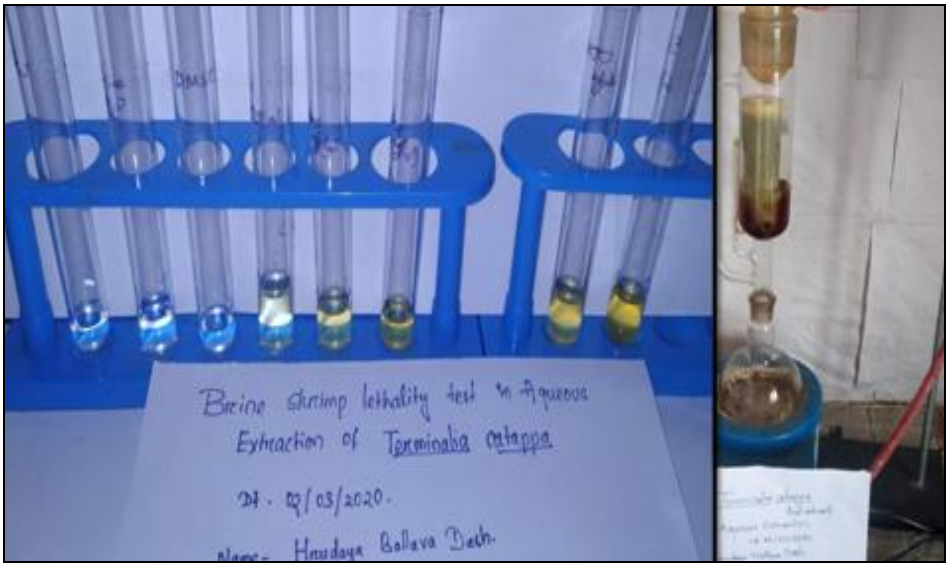

FIG. 1: CYTOTOXICITY TEST OF EXPERIMENTAL PLANT

The aqueous extract of *C. roxburghii* Spreng., all brine shrimp dead in concentration 500 g/ml, some dead in 400 g/ml, 300 g/ml, 200 g/ml and 100 g/ml. Their % of lethality were 100% -500 g/ml, 90% - 400 g/ml, 80% - 300 g/ml, 200 g/ml, 100 g/ml **Table 6.**

TABLE 6: TOXICITY TEST OF *C. ROXBURGHII* SPRENG. (AQUEOUS EXTRACT)

Sample		Time									% of inhibition
		10 min	20 min	30 min	60 min	2 h	3 h	4 h	18 h	24 h	
Aqueous extract	500 g/ml	+4	+4	+4	+4	0	0	0	0	0	100
	400 g/ml	+4	+4	+4	+4	+3	+3	+3	+2	+1	90
	300 g/ml	+4	+4	+4	+4	+4	+4	+4	+3	+2	80
	200 g/ml	+4	+4	+4	+4	+4	+4	+4	+2	+2	80
	100 g/ml	+4	+4	+4	+4	+4	+4	+4	+2	+2	80
Distilled water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Brine water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
5% DMSO		+4	+4	+4	+4	+4	+4	+4	+4	+4	0

In acetone extract of *Combretum roxburghii* Spreng. all the brine shrimps survived in distilled water, brine water, 5% DMSO and dead in 500 g/ml. The % of lethality were 100 % - 500 g/ml, 80 % - 400 g/ml and 70 % - 300 g/ml, 200 g/ml **Table 7.**

TABLE 7: TOXICITY TEST OF *C. ROXBURGHII* SPRENG. (ACETONE EXTRACT)

Sample		Time									% of Inhibition
		10 min	20 Min	30 Min	60 Min	2 h	3 h	4 h	18 h	24 h	
Acetone extract	500 g/ml	+4	+4	+4	+4	+3	+3	+3	0	0	100
	400 g/ml	+4	+4	+4	+4	+4	+3	+3	+3	+2	80
	300 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	+3	70
	200 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	+3	70
	100 g/ml	+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Distilled water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Brine water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
5% DMSO		+4	+4	+4	+4	+4	+4	+4	+4	+4	0

The methanolic extract of *Combretum roxburghii* Spreng. Indicated the highest cytotoxic activities to brine shrimp. In this extract all the brine shrimp dead in concentration of 500 g/ml, 400 g/ml, 300 g/ml, 200 g/ml, 100 g/ml **Table 8.** Other researchers also reported the anticancer activity using other models & methods [44, 45].

TABLE 8: TOXICITY TEST OF *C. ROXBURGHII* SPRENG. (METHANOL EXTRACT)

Sample		Time									% of Inhibition
		10 min	20 Min	30 min	60 Min	2 h	3 h	4 h	18 h	24 h	
Methanol Extraction	500 g/ml	+4	+4	+2	+1	+1	0	0	0	0	100
	400 g/ml	+4	+4	+4	+3	+2	+1	+1	0	0	100
	300 g/ml	+4	+4	+4	+3	+2	+1	+1	0	0	100
	200 g/ml	+4	+4	+4	+3	+2	+1	+1	0	0	100
	100 g/ml	+4	+4	+4	+4	+4	+3	+2	0	0	100
Distilled water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
Brine water		+4	+4	+4	+4	+4	+4	+4	+4	+4	0
5% DMSO		+4	+4	+4	+4	+4	+4	+4	+4	+4	0

TABLE 9: TOTAL PHENOL & TANNIN ESTIMATION IN AQUEOUS EXTRACT OF EXPERIMENTAL PLANT PARTS

Plant parts (Leaf)	Tannin (Microgram/mg)	Total Phenol (Microgram/mg)
C. roxburghii Spreng.	0.300	0.451
T. catappa L.	0.650	0.289

Phytochemical screening tested under different solvent as aqueous, methanol, ethanol and acetone. Secondary metabolites were detected in different extracts of the plant, which indicates the sound anticancer activity. Among these two plant species, the maximum bioactive compounds were detected in *Terminalia catappa* L. in methanol, ethanol, acetone extract as compared to *Combretum roxburghii* Spreng.

In the lethality test, the maximum percentage of inhibition was observed in acetone extract of *Terminalia catappa* L. and methanol extract of *Combretum roxburghii* Spreng. The quantitative estimation of total phenol and tannin also indicates that selected plant parts might be sound anti-cancer agents **Table 9.** Tannin isolated from *Terminallia catappa* L. also has antioxidant activities [45].

CONCLUSION: The whole world is facing problems of viral diseases. The malpractices of drugs and biodiversity loss created lots of novel pathogens, but drugs are going to fail. Therefore, there is an urgent need to screen new compounds from the wild. The present study provides baseline data in this line of research on plants belonging to the Combretaceae family. The selected plant parts are rich with diverse bioactive compounds and have good cytotoxic activity against *Artemia salina,* which indicates the preventive potentials against cancer.

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