Novel Bioactive Molecules

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CHAPTER 6

XANTHIUM PLANTS – GOOD SOURCES OF ANTICANCEROUS BIOACTIVE AGENTS

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Since the dawn of human creation, diseases, decay and death have coexisted with life and has been threatening mankind.

During mid of 20th century average life expectancy in our country was around 30 years and with the advancement of medicinal research, today, it has reached 64 years. Coronary artery disease is the leading cause of death world wide. Annual death from CAD in India raised from 2.26 million (1990) to 4.77 million (2020). Adults aged 30-79 years with hypertension increased from 650 million to 1.28 billion in last thirty years. Nearly 10 million deaths caused by cancer in 2020. There were 18.1 million cancer cases around the world in 2020. Tuberculosis is the 13th major cause of death and 2nd leading infectious killer. 23% of world population was infected by Tuberculosis in 2018.

CARCINOMA is the term used to explain all malignant tumors or neoplasms regardless of their origin. Cancers are divided into two main classes (i) malignant tumors which arise from epithelial tissue, are called carcinomas and (ii) those arising from connective or supportive tissue are called sarcomas.

To provide quick relief to ailing humanity, this subcontinent also adopted European system of medicine which got enormous progress in recent years. But with the advent of modern allopathic system of medicine its ill effects also started.

Thus the prolong use of modern drugs and their after effects specifically of some powerful antibiotics have compelled the scientists look for the entire genera of medicinal flora, available in Indian sub-continent, because due to its varied climatic conditions, our nation is bestowed with the rich medicinal flora.

Enough evidences are there for the use of herbal plants for the treatment of various diseases including CANCER, for centuries. A complete survey of literature reveals about the use of a good number of Indian plants, which have good reputation as anticancer agents e.g. Vincristine and Vinblastine have been found to be effective in some early stages.

All ancient civilizations of the world, be it Indian or Chinese, Egyptian or Peruvian, contain records of a rich materia medica of their own, yet in the interest of mankind. More therapeutic newer drugs have been rediscovered from our ancient heritage by

diligent workers using modern pharmacological laboratory and clinical studies, thereby providing possibility of yielding more and more new worthwhile remedies for the alleviation and treatment of many diseases for which no useful cures are yet known and no laboratory can claim to have obtained complete expertise in this respect.

Various plant constituents such as sesquiterpene lactones have been thoroughly investigated for their reputation as anticancer drugs. During the survey of available literature on carcinoma it has been found that about 1400 anticancer plants have been studied for their different aspects. For example podophyllum was the first to be used as an anticancer drug about 2000 years ago by the ancient chinese. The alkaloids of Vincarosea i.e. Vincaleukoblastine and Vincristine are found to be effective in certain forms of malignant neoplastic conditions of man. Camptothecin and its derivatives, alkaloids from the chinese tree Camptotheca acuminata is reported to be used for the treatment for cancer in China. Brueantine, which is isolated from Brucea antidysenterica is used in Ethopia for the treatment of cancer which showed high antitumor activity at low dosages with most of side effects.

There exists enough examples of use of large number of ses quiterpenoidal lactones have been isolated and identified during the period of continuing search for antitumor agents of plant origin. During the past 30 years over 500 sesquiterpene lactones have been isolated, mainly from plants belonging to compositea (Asteraceae) family.

Classification :

The sesquiterpene lactones are colourless, bitter, relatively stable, lypophilic constituents biogenetically derived from trans farneysl pyrophosphate following an initial cyclisation and subsequent oxidative modifications. The major types of lactones resulting from enzyme-mediated cyclisations are classified primarily on the basis of their carbocyclic skeleton :

1. Guainolides
2. Eudesmanolides
3. Pseudoguainolides
4. Eremophilanolides
5. Xanthanolides

Structure and Activity :

Sesquiterpenoidal lactones are the group of compounds considerd as anticancer agents due to their potent biological activities including cancer cell cytotoxicity and antineoplastic efficacy in in vivo studies. In clinical trials Artimisinin, parthanolides and other synthetic derivatives are selective towards tumor and cancer stem cells by targeting specific signaling pathways. They reduce harm by microbial attack by disruption of microbes cell membrane. Alpha-beta unsaturated lactone moiety acts as Michael acceptor and reacts with nucleophiles in enzymes and other proteins

alkylating them irreversibly which disrupt the function of macromolecules due to steric changes.

Enough evidences are there that the several cytotoxic sesquiterpenes contain alpha methylene gama lactone ring. During study of the structure-activity relationship among sesquiterpenes lactones it was noted that the presence of exocyclic double bond conjugated to the γ–lactone was essential for cytotoxicity. Sesquiterpene lactones which incorporate a cyclopentenone or a-methylene lactone (in addition to the α,β–methylene- γ-lactone) appear to produce enhanced cytotoxicity. Thus an examination of sesquiterpene lactones indicates that following structural configurations are the principal requirements for antitumor and cytotoxic activities which are essentially tested.

i. The presence of a functional group such as an epoxide, hydroxyl, chlorohydrin, unsaturated ketone which enhances the reactivity of the conjugated lactone towards biological nucleophiles.

ii. The presence of an exocyclic methylene conjugated to a γ-lactone associated with cyclopentenone ring.

Few recently investigated sesquiterpenes lactones of plant origin of different xanthium plants are tabulated in Table : 1.

Table - 1

S.No.	Plant	XANTHANOLIDE
1	Xanthium strumarium	Xanthumin
2	Xanthium strumarium	8-epi-xanthatin
3	Xanthium strumarium	Xanthinin
4	Xanthium strumarium	Xanthumanol
5	Xanthium strumarium	Xanthatin
6	Xanthium strumarium	Xanthinosin
7	Xanthium occidentale	Xanthumin
8	Xanthium indicum	2-epi-xnathanol
9	Xanthium indicum	Tomentosin
10	Xanthium spionosum	Desacetyl xanthiminol
11	Xanthium spionosum	Xanthatin
12	Xanthium penslyvanicum	Xanthinin

Spectral Study :

Spectroscopy has established its place in the structure elucidation of Xanthanolids because their significant structural features can be proved by spectroscopical data and by the critical examination of their spectra. Position of the IR bands at 1687, 1605, 1595 cm^{-1} clearly show the presence of α,B, γ,δ unsaturated dienone system while IR band at 1765 cm^{-1} indicates that the latter is a part of γ-lactone moiety. Besides this IR band between 1630-1690 cm^{-1} show the presence of > C = C, - C = O in these lactones; whereas by the ^1H-NMR spectra of sesquiterpene lactones, α methylene- γ-lactone moiety is confirmed by two one proton doublets at δ 6.20 (H-13a) and δ 5.58(H-13 b) and a proton multiplet at δ 3.53 (H-7).

On the other hand the unsaturated lactone is either cis or trans fused to the C_6-C_7 or C-C_8 positions of the carbocyclic skeleton. The double bond E geometry and the relative stereochemistry at C-7, C-8 and C-10 are determined by analysis of the coupling constants for ring protons. It is also indicated that the cycloheptane ring must exist predominatly in distorted boat conformation carrying a pseudoequatorially oriented methyl group at C-10 in Xanthanolids.

Extraction :

The Xanthanolides are isolated and characterised as : First the plants are dried, powdered and then extracted by solvents of increasing polarities petroleum ether, benzene, ethyl acetate, acetone, chloroform & methyl alcohol and ethyl alcohol.

Detection :

Various crude extracts thus obtained are filtered and concentrated under reduced pressure. The presence of sesquiterpene lactones is detected by following tests and colour reactions as described below :

(A)

Colour Reactions

(i) A red colour is obtained when sesquiterpene lactone is treated with dil HCl and resorcinol in a test tube.

(ii) A red colour is produced when the sesquiterpene lactone is heated with 1ml of 50% H_2SO_4 and two drops of aq. $FeCl_3$ in it.

9iii)

A rose red colour is obtained when small quantity of compound is treated with 10% alc. KOH solution in the test tube.

(B) Hydroxamic Test

The compound to be tested for Xanthonalide is taken in small quantity and dissolved with acetone in a porcelin crucible. To this 2,3 drops of alcoholic hydroxyl amine hydrochloride solution and few drops of saturated alc. KOH are added. the mixture is heated till the reaction starts. Then the mixture is cooled and acidified with HCl. A drop of 1% $FeCl_3$ solution is added, when a violet coloured is obtained which shows the presence of lactone ring in the compound.

The above extracts showing the presence of sesquiterpene lactone are subjected to column, GLC and other chromatographic techniques (PC, TLC, CC) for the isolation of pure sesquiterpenoidal lactones. The isolated sesquiterpenoidal lactones are then subjected to degradative analysis (acetylation, methylation, hydrolysis, reduction etc.) for their conversion into known sesquiterpenoidal lactones as identified by mixed m.p. and super imposable spectra.

Conclusion :

From the available literature it has been found that amongst the anticancerous plants, Xanthium plants also possess a good reputation. A deep survey of literature indicates that various species of Xanthium plants which belong to composite family, have various Xanthanoloid constituents may be effectively used in curing various forms of cancer.

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