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Natural Products Reported as Potential Inhibitors of Uterine Cervical Neoplasia

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SUMMARY. The present work is a literature review of crude plant extracts, semi-purified fractions and chemically defined molecules with potential antitumor activity against uterine cervical neoplasia. The review refers to 36 plants with their families, geographical distribution, parts used, type of extract used, and their activity. It also includes the activity found in 27 compounds isolated from higher plants and microorganisms, which are classified in appropriate chemical groups. Some aspects of recent research with natural products directed to the eventual production of drugs which are inhibitors of uterine cervical neoplasia are discussed.

RESUMEN. "Productos naturales que son potenciales inhibidores de neoplasias de cuello uterino". El presente trabajo consiste en una revisión de la literatura, con respecto de drogas vegetales, extractos semipuros y substancias químicamente definidas, con actividad potencial para casos de neoplasia de cuello uterino. Esta revisión incluye 36 plantas,las familias, área geográfica, partes utilizadas, tipos de extracto y la actividad encontrada. Incluye también 27 substancias aisladas de plantas superiores y microorganismos, clasificados en grupos químicos adecuados. Son discutidos algunos aspectos recientes de la investigación de productos naturales dirigidos a la obtención de medicamentos que inhiben neoplasias del cuello uterino.

INTRODUCTION

The ten leading causes of death in the United States of America are listed in Table 1. Topping the list are heart disease and cancer. In 1995, these diseases were estimated as responsible for the annual economic burden of $137.7 billion and $104 billion dollars, respectively [1]. Due in part to the significant decrease in the annual death rate due to heart diseases with simultaneous increase in the death rate due to certain types of cancer, it is generally accepted that the latter will be the leading cause of death in the new millenium. Thus, the search for new anticancer agents, specially those effective against breast, ovarian, prostate, lung, colon and uterine cervical cancers, is a top priority in developed countries.

Carcinoma of the cervix is the second most common malignant neoplasia among women, following breast cancer. Approximately 500.000 new cases of cervix cancer are diagnosed worldwide each year [2]. Its etiology, like all other cancers, remains unclear at this time. A relationship between herpes virus type 2 and human papillomavirus infections and invasive carcinomas of the cervix has been suggested [3-5]. The basis for this suggestion is the observation that these viruses are present in a much higher percentage in patients with carcinoma of the cervix than in a comparable control group of

KEY WORDS: Anticancer agent, Antitumor activity, Cancer, Natural products, Uterine cervical neoplasia, Uterus cervix, Tumor.
PALABRAS CLAVE: Actividad antitumoral, Agente anticancerígeno, Cáncer, Cuello uterino, Neoplasia cervical uterina, Productos naturales, Tumor.

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Cause of death	Deaths per 100,000	Cost USD (billion)
Heart disease	189.8	137.7
Cancer	135.0	104.0
Accidents	32.5	-
Asthma	19.7	6.2
Pneumonia	14.0	-
Infectious and parasitic diseases	12.0	-
Diabetes mellitus	11.7	91.8
Suicide	11.5	-
Homicide	10.7	-
Chronic liver disease	8.6	

Adapted from reference 1

Table 1. Leading causes of death in USA and annual economic burden.

women. Uterine cervical cancer has also often been correlated with race, with the rate of invasive cancer of the cervix found to be twice as great in black females [6]. This, however, is possibly explained by the fact that this disease tends to occur more frequently in educationally and socioeconomically underprivileged women and may not be due to inherent biological factors [7]. There has been much speculation on a possible relationship between early and frequent sexual activity and the incidence of uterine cervical cancer, though supporting evidence is by no means conclusive. Smoking appears to double the risk of uterine cervical cancer [8]. Some studies have found a significantly increased risk of uterine cervical neoplasia in women who use contraceptive pills [9]. The claim, however, is not supported by other studies [10].

Chemopreventive agents are of great interest since they may reduce the incidence of cancer in human populations. There are numerous references in the scientific literature about the relationship between vegetable and fruit consumption and the risk of cancer. It has been estimated that up to 70% of all cancer is associated with the type of diet [11]. Major dietary hypotheses include a relationship between high fat consumption and breast and colorectal cancers; high alcohol intake and respiratory, gastrointestinal, breast, and liver cancers; and low fiber intake and colorectal cancer. Substances present in vegetables and fruits that may help to protect against uterine cervical dysplasia include *trans*-retinoic acid and folic acid. For further details on this subject, the original references should be consulted [12,13].

In a previous paper we have presented a review on crude plant extracts and chemically defined molecules with potential antitumor activity for mammary [14], prostate [15] and ovarian neoplasias [16]. In this work we have reviewed the literature related with the natural products that act specifically inhibiting the neoplasia of the cervix.

The search was carred out on Chemical Abstracts, Biological Abstracts and the data bank of The University of Illinois in Chicago - NAPRALERT (Acronym for Natural Products ALERT), updated to April 2000, using uterine cervical plus tumor as legends. The references found in the search were later consulted.The search for data in different sources led in the elaboration of a list of natural products evaluated specifically for uterine cervical neoplasia (Tables 2 and 3). It should be noted that most of the references cited are not first hand observations, but compilations copied from other sources. The original references should be consulted for details on the models or mechanism based bioassays used for testing plant extracts and pure compounds against uterine cervical tumors.

PLANTS INHIBITING UTERINE CERVICAL NEOPLASIA

It is well known that China is one of the leading nations in the use of medicinal plants. It has a long history of the use of herbal medicines. The accumulated vast experience has frequently demonstrated conspicuous and unique effects on certain diseases with generally few toxic and other undesirable side-effects [17]. Of thirty six crude plant extracts and their semi-purified fractions described in the literature which are used in the treatment of cancer of the cervix, only nine plants used are not of Chinese origin (see Table 2).

Wu [18] discovered the efficacy of a famous Chinese prescription, “Kung Ching Tang” for the treatment of uterine cervical neoplasia. It is produced in the form of pills which contain a mixture of eleven Chinese traditional drugs, obtained from *Achyranthes bidentata, Angelica sinensis, Coix lacryma-jobi, Curcuma zedoaria, Cyperus rotundus, Dipsacus asper, Laminaria japonica, Prunela vulgaris, Prunus persica, Sparganium stoloniferum,* and *Vaccaria segetalis.* In 52.9% of cases treated with this natural medicine the symptoms completely disappeared and in 27.2% the tumors were reduced in size. The plants are listed in Table 2.

PLANT	FAMILY	ORIGIN	PART USED	EXTRACT	RESULT	REFERENCE
Achyranthes bidentata	Amaranthaceae	China	Root	Aqueous extract	Active	18
Agrimonia pilosa	Rosaceae	China	Whole plant	Aqueous extract	Active	25
Angelica sinensis	Apiaceae	China	Root	Aqueous extract	Active	18
Arctotis auriculata	Compositae	South Africa	Leaf	Type ext not stated	Active	26
Bletilla striata	Orchidaceae	China	Tuber	Aqueous extract	Active	27
Brucea javanica	Simaroubaceae	China	Seed	Seed oil	Active	28
Carapa guianensis	Meliaceae	Brazil	Seed	Seed oil	Active	29
Chelidonium major	Papaveraceae	Austria	Whole plant	Alkaloid fraction	Active	30
Clerodendrum bungei	Verbenaceae	China	Whole plant	Alkaloid fraction	Inactive	27
Codonopsis nervosa	Campanulaceae	China	Root	Type ext not stated	Active	31,32
Coix lacryma-jobi	Poaceae	China	Seed	Aqueous extract	Active	18
Crotalaria assamica	Fabaceae	China	Whole plant	Alkaloid fraction	Active	27
Crotalaria juncea	Fabaceae	China	Seed	Alkaloid fraction	Active	27
Crotalaria sessiliflora	Leguminosae	China	Whole plant	Type ext not stated	Active	31,32
Curcuma zedoaria	Zingiberaceae	China	Rhizome	Aqueous extract	Active	18
Cyerus rotundus	Cyperaceae	China	Seed	Aqueous extract	Active	18
Dioscorea collettii	Dioscoreaceae	China	Rhizome	Type ext not stated	Active	33
Dipsacus asper	Dipsacaceae	China	Root	Aqueous extract	Active	18
Ficus pumila	Moraceae	China	Fruit	Aqueous extract	Active	27
Glycyrrhiza glaba	Fabaceae	Japan	Root	Type ext not stated	Active	34
Hypoxis nyasica	Hypoxidaceae	Malawi	Tuber	Type ext not stated	Active	35
Hypoxis rooperii	Hypoxidaceae	Swaziland	Tuber	Type ext not stated	Active	36
Kigelia africana	Bignoniaceae	Malawi	Rootbark	Type ext not stated	Active	37
Laminaria japonica	Laminareaceae	China	Thallus	Aqueous extract	Active	18
Lepechinia spicata	Labiatae	Mexico	Part not specified	Type ext not stated	Active	38
Lysimachia clethroides	Primulaceae	China	Whole plant	Flavonoid fraction	Active	27
Marsdenia tenacissima	Asclepiadaceae	China	Stem	Aqueous extract	Active	27
Patrinia scabra	Valerianaceae	China	Root	Type ext not stated	Active	39
Pelargonium graveolens	Geraniaceae	China	Whole plant	Essential oil	Active	31,32
Prunella vulgaris	Lamiaceae	China	Fruit	Aqueous extract	Active	18
Prunus persica	Rosaceae	China	Seed	Aqueous extract	Active	27
Sagina japonica	Caryophyllaceae	China	Whole plant	Flavonoid fraction	Active	40
Sparganium stoloniferum	Sparganiaceae	China	Rhizome	Aqueous extract	Active	18
Tabebuia rosea	Bignoniaceae	Mexico	Bark	Type ext not stated	Active	41
Vaccaria segetalis	Caryophyllaceae	China	Seed	Aqueous extract	Active	18
Xylosma congesta	Flacourtiaceae	China	Bark	Type ext not stated	Active	27

Table 2. Plants inhibiting uterine cervical neoplasias

CHEMICAL NAME	CLASS	ORGANISM TESTED	RESULT	REFERENCE
Abrin	Protein	Human	Active	42
Adriamycin	Non-alk N-heterocycle	Human	Active	19
Adiantifoline, methoxy	Alkaloid	Mouse	Active	43
Asparagoside B	Sapogenin	Mouse	Inactive	44
Asparagoside C	Sapogenin	Mouse	Active	44
Asparagoside D	Sapogenin	Mouse	Active	44
Asparagoside E	Sapogenin	Mouse	Inactive	44
Asparagoside F	Sapogenin	Mouse	Inactive	44
Asparagoside G	Sapogenin	Mouse	Inactive	44
Asparagoside H	Sapogenin	Mouse	Inactive	44
Bleomycin	Non-alk N-heterocycle	Human	Active	45
Colchicinamide	Alkaloid	Not stated	Active	17
Curcumol	Sesquiterpene	Not stated	Active	17
Curdione	Sesquiterpene	Not stated	Active	17
Curzerenone	Sesquiterpene	Human	Active	46
Echinomycin	Non-alk N-heterocycle	Human	Active	47
Irinotecan	Alkaloid	Mouse	Active	48
Iriquinone	Quinoid	Mouse	Active	49
Mitomycin C	Alkaloid	Human	Active	20
Pallasone A	Quinoid	Mouse	Active	50
Puqietinone	Alkaloid	Mouse	Active	51
Quercetin	Flavonoid	Mouse	Active	52
Retinoic Acid	Carotenoid	Mouse	Active	53
Sophocarpine	Alkaloid	Mouse	Active	54
Tetrandrine, (+)	Alkaloid	Mouse	Active	43
Vincaleukoblastine	Alkaloid	Human	Inactive	55
Vincristine	Alkaloid	Human	Active	19

Table 3. Chemically defined molecules inhibiting uterine cervical neoplasias.

CHEMICALLY DEFINED MOLECULES INHIBITING UTERINE CERVICAL NEOPLASIA

Twenty seven chemically defined natural molecules have been reported in the literature as useful for the treatment of uterine cervical neoplasia (Table 3). Only four, *viz.*, adriamycin (doxorubicin), bleomycin A_2, mitomycin C and vincristine, are currently used clinically in the chemotherapeutic treatment of the disease [19,20]. Of the twenty seven active compounds which have been isolated and identified, nine are alkaloids, seven sapogenins, three non-alkaloidal *N*-heterocycles, three sesquiterpenes, two quinoids, one flavonoid, one carotenoid and one protein.

Adriamycin is an antibiotic belonging to the group of the anthracyclins isolated from cultures of *Streptomyces peuceutius* variety *caesius*. The mechanism of action of adriamycin, although it is not completely elucidated, appears to be related with its ability to bind to DNA and to inhibit the synthesis of nucleic acid. It is indicated in the treatment of a broad-spectrum of carcinomas, including bladder, breast, cervix, endometrium, ovary, pancreas, prostate and testicular cancers [21].

Bleomycins are a class of glycopeptide antitumor antibiotics which were isolated by Umezawa and co-workers from *Streptomyces verticelus* over 30 years ago [22]. Bleomycin A_2, which differs from other naturally occurring bleomycins only in the cationic C-terminus, is the major component (70%) of the clinical anticancer drug Blenoxane, which is used for the treatment of carcinomas of the skin, cervix, vulva, penis and testicles, head and neck *inter alia* [21,23]. Each structural unit of bleomycin A_2 has been shown to cleave RNA as well as DNA-RNA

hybrids, which provide additional nucleic acid targets potentially related to its biological properties [23].

Mitomycin C is a pyrrolizidine alkaloid isolated from *Streptomyces caespitosus.* It is activated by intracellular reductases, forming a bifunctional or trifuncional alkylating agent, whose cross linking of the DNA inhibits its synthesis and, to a lesser degree, that of RNA and of protein. It is indicated in the palliative treatment, in association with other antineoplastic agents, of stomach or pancreas adenocarcinoma which do not respond to surgery and/or radiotherapy, carcinoma of the bladder, biliary and uterine cervical carcinoma, among others [21].

Vincristine was isolated in 1949 by Canadian researchers at the University of Western Ontario from periwinkle *(Catharanthus roseus),* a plant which had been used for many years to treat diabetes mellitus in the West Indies. Scientific work showed that the plant extract reduced levels of white blood cells and caused granulocytopenia when given intravenously. These toxic effects are commonly found with many antitumor drugs. The active principle was eventually purified and named vincristine. Although many other alkaloids have been isolated from *C. roseus,* only vincristine and vinblastine have been developed for clinical use. The antiproliferative activity of these two compounds is related to their specific interaction with tubulin; preventing assembly of tubulin into microtubules and arresting cell division. Vincristine is used mainly in combination with other anticancer

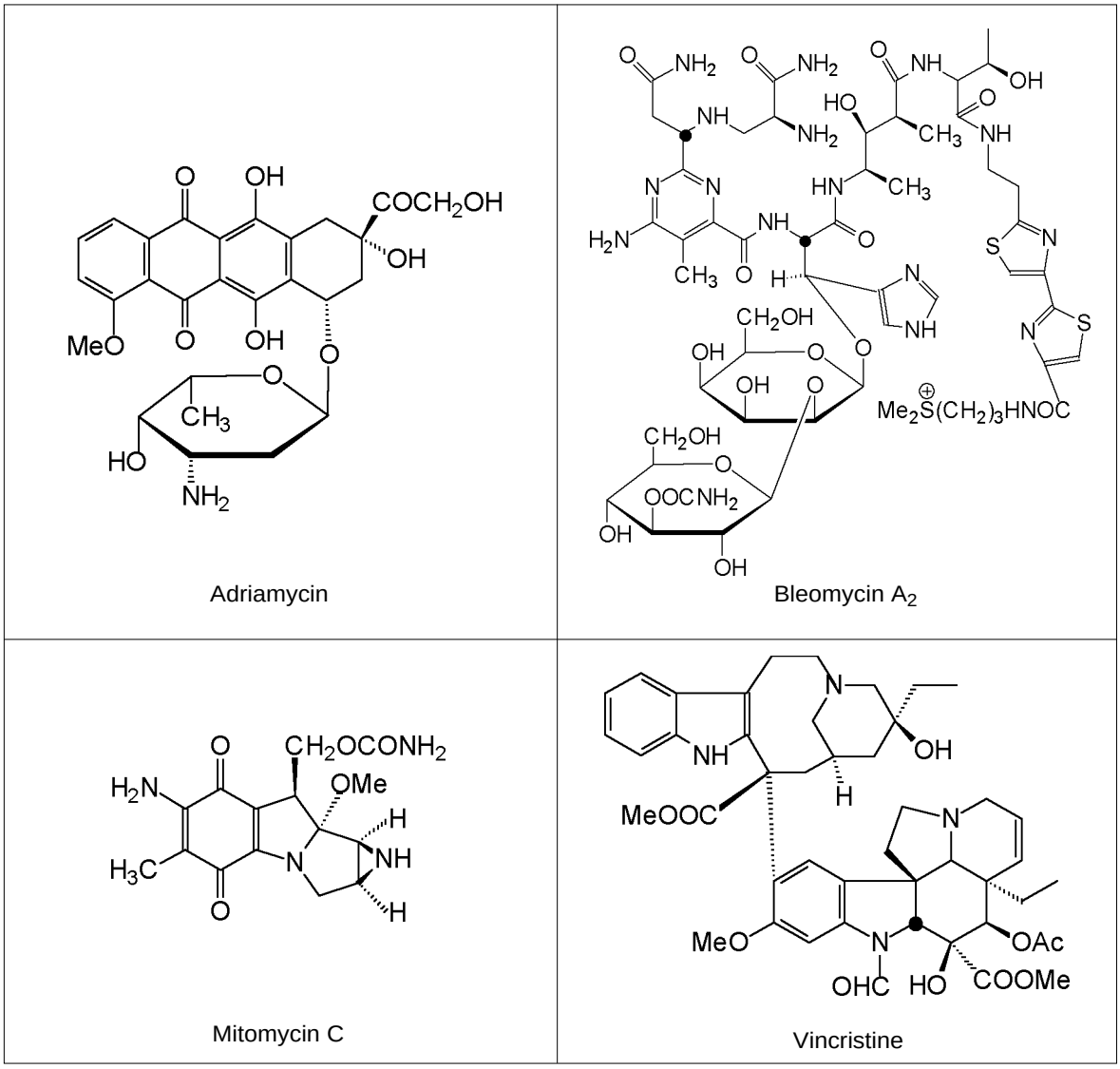

Figure 1. Chemical structures of the most representative natural products used in the treatment of uterine cervical neoplasia.

drugs for the treatment of acute lymphocyte leukemia in children, uterine cervical, colon, breast, ovarian and other carcinomas [21,24].

The results of the literature survey are presented in Table 3. In Figure 1 the chemical structures of the most representative natural products used in the treatment of uterine cervical neoplasia are presented.

CONCLUSION

We can conclude that in spite of the large incidence of uterine cervical neoplasia suffered by women all over the world, there has been no organized information in the literature about the use of products of natural origin, which inhibit this pathology. Furthermore, there is a large variety of plants and microorganisms in our planet yet to be explored and, thus, there is potential for attaining a stage in the future when uterine cervical neoplasia will no longer be a threat.

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