Borneo Journal of Pharmacy
Vol 5 Issue 1 February 2022
Page 71 – 80

http://journal.umpalangkaraya.ac.id/index.php/bjop/article/view/3052
DOI: https://doi.org/10.33084/bjop.v5i1.3052
e-ISSN: 2621-4814

Mini Review

Cancer Statistics and Anticancer Potential of *Peganum harmala* Alkaloids: A Review

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Keywords:
Alkaloids
Cancer
Peganum harmala
Statistics

Abstract

Cancer is one of the most common diseases in the world. Although it develops in various organs and tissues, some species maintain a stable position in the ranking. Although the cancer causes are different, the specific grounds for each type are also noted. Sometimes the increase in incidents and mortality is associated with geographical reasons. Increases in statistics, expensive and chemotherapeutic methods focus on plant-based substances. One of such potential plants is *Peganum harmala*, which contains alkaloids such as harmine, harmaline, harmol, and harmalol. The effects of these compounds on many cancer cells have been tested, and positive results have been obtained. This fact reinforces the claim that more in-depth research on noted alkaloids is needed.

Received: December 28th, 2021
Revised: February 9th, 2022
Accepted: February 18th, 2022
Published: February 28th, 2022

INTRODUCTION

Cancer is one of the most dangerous diseases in the modern world. The reasons for its formation and the causing factors are different. Carcinogenic substances in the food we eat in modern life, the air we breathe, and the water we drink lead to this disease's greater spread. Chemical additives used in foods for long-term storage, especially nitrites in meat products; aflatoxins, pesticides that we come across as contaminants; toxic gases emitted from factories, machines; toxic wastes released into the water, heavy metals, water pollutants such as arsenic can be a typical example for our problem[1-3]. At the heart of the growing prevalence of this disease are also some of our addictions, such as smoking and alcohol[4]. Numerous studies have been conducted on the effects of smoking and alcohol consumption on cancer statistics, and it has been found that there is an increasing dependence graphic between these behaviors and cancer incidence and mortality rates[5,6].

The above are just some of the cancer causes. Even if we want to get rid of pollution around the world one day, even if we want to give up our addictions such as smoking and alcohol, reducing cancer would still take time. If we add genetic factors to these causes, we can see that we can not escape from this disease[7]. Therefore, besides eliminating the causes of the disease as much as possible, it seems to be the most logical way to find new therapeutical ways of fighting it. Many anti-cancer drugs are used today, and the exacerbation of the disease statistics leads to an increase in the substance choices used in its treatment and the search for new alternatives in this direction. The effects of many synthetic chemicals and plant-based compounds on various cancer cells have been studied, and this process continues to be relevant today[8]. There are specific drugs currently used in the body to slow down cancer. However, they are expensive and relatively difficult to reach[9]. For such an increasing rate of disease, more accessible sources are needed. In this case, the plants and plant-based compounds come to the fore. Some plants are especially noteworthy for their anti-cancer effects, making their usage potential closer to reality. One such plant is *Peganum harmala*[10].

Although its leaf extract is used in practice as an anti-cancer agent in Iran, the use of *P. harmala* is not widely spread around the world[11]. The effects of its most predominant compounds - alkaloids such as harmine, harmaline, harmol, and harmalol

on many cancer cell lines have been separately studied and obtained favorable results. Moreover, this plant is found on almost all continents, especially in Asia and Africa. Moreover, it does not require special care for growing and maturing; its primary habitat is arid and saline soils. Because it is so accessible to humans, its traditional use also has an extensive list[12]. However, despite all these properties, effectiveness, and availability, none of these plant alkaloids are used to prevent cancer. Thus, this article aims to stimulate more research on new natural alternatives, such as *P. harmala* alkaloids, and raise awareness of their therapeutic potential when the incidence and mortality of cancer are increasing.

CANCER STATISTICS

Lung cancer has been linked to tobacco usage in 90% of male and 79% of female patients. Smoking is thought to be responsible for 90% of lung cancer fatalities. Compared to non-smokers, lifelong smokers have a 20-40 times higher risk of developing lung cancer[13]. Men's mortality and incidence rates are nearly two times higher than women. Smoking is responsible for almost two-thirds of lung cancer deaths globally. It is known that men are more likely to drink alcohol, so the effects of alcohol on cancer are more intense. According to 2020 data, most alcohol-related types in men have been reported with esophageal, liver, and breast cancer[14].

It is a fact that there are social reasons besides just those related to the environment and our routines. For instance, in low- and lower-middle-income nations, cancer-causing diseases such as hepatitis and human papillomavirus (HPV) account for roughly 30% of cancer cases. Also, in these nations, late-stage presentation and lack of access to diagnosis and treatment are prevalent. According to reports, comprehensive therapy is available in more than 90% of high-income countries but fewer than 15% in low-income countries[15].

There are many types of cancer, depending on the organ and tissue in which they are located, but some differ significantly in terms of prevalence and mortality. Based on information for 36 cancers in 185 countries in 2020, the cancer types with the highest incidence and mortality are shown in **Table I**. When we compare the statistics of cancer types worldwide, we see that certain regions and countries are particularly conspicuous. The regions and countries with the highest prevalence and mortality rates are shown in **Table II**.

Table I. The most common cancer types in 2020[14]

Incidence		Mortality	
Cancer type	**Rate (%)**	**Cancer type**	**Rate (%)**
Female breast	11.7	Lung	18
Lung	11.4	Colorectal	9.4
Colorectal	10.0	Liver	8.3
Prostate	7.3	Stomach	7.7
Stomach	5.6	Female breast	6.9

Table II. Prevalence of cancer types by regions and countries in 2020[14]

Cancer type	Highest incidence		Highest mortality	
	Region	**Country/its region**	**Region**	**Country/its region**
Female breast	Australia/New Zealand	Belgium/Western Europe	Melanesia	Barbados/Caribbean
Lung	Micronesia/Polinesia	Turkey/Western Asia	Nothern America	Hungary/Eastern Europe
Colon	Southern Europe	Hungary/Eastern Europe	Australia/New Zealand	Norway/Northern Europe
Rectum	Eastern Europe	Portugal/Southern Europe	Eastern Europe	Latvia/Northern Europe
Prostate	Northern Europe	Ireland/Northern Europe	Caribbean	Zimbabwe/Eastern Africa
Stomach	Eastern Asia	Japan/Eastern Asia	Eastern Asia	Mongolia/Eastern Asia
Liver	Eastern Asia	Mongolia/Eastern Asia	Northern Africa	Mongolia/Eastern Asia
Oesophagus	Eastern Asia	Cape Verde/Western Africa	Eastern Asia	Malawi/Eastern Africa
Cervix uteri	Eastern Africa	Malawi/Eastern Africa	Eastern Africa	Malawi/Eastern Africa
Thyroid	Northern America	Cyprus/Southern Europe	Micronesia/Polinesia	Cyprus/Southern Europe
Bladder	Southern Europe	Greece/Southern Europe	Southern Europe; Western Europe	Hungary/Eastern Europe
Non-melanoma skin	Australia/New Zealand	Australia/ Australia/New Zealand	Australia/ Australia/New Zealand	Australia/New Zealand
Pancreas	Eastern Europe	Hungary/Eastern Europe	Western Europe	Hungary/Eastern Europe
Non-Hodgkin lymphoma	Australia/New Zealand	Israel/Western Asia	Australia/New Zealand; Northern America	Slovenia/Southern Europe
Corpus uteri	Northern America	Poland/Eastern Europe	Eastern Europe	Bahamas/Caribbean
Kaposi sarcoma	Southern Africa	Mozambique/Eastern Africa	Southern Africa	Zambia/Eastern Africa
Lip, oral cavity	Melanesia	Papua New Guinea/Melanesia	Melanesia	Papua New Guinea/Melanesia

Unfortunately, the cancer tumor, which has become so entrenched in human life today, will grow even bigger in 20 years. Forecasts show that in 2040, the highest increase in cancer rates will be in Africa (incidence +89.1%, mortality +92.9%), and the lowest increase will be in Europe (incidence +21.0%, mortality +29.2%) (**Table III**)[16]. According to the incidence data, the most common cancer types will be breast, melanoma, and lung; and in terms of mortality, lung, liver, intrahepatic bile duct, and colorectal cancer will take the first three places.

Table III. Predicted cancer growth rates in 2040[16]

Region	Incidence (%)			Mortality (%)		
	Both	Female	Male	Both	Female	Male
Africa	89.1	86.2	92.9	92.9	90.2	96.1
Latin America, Caribbean	65.6	59.0	72.5	77.3	72.7	81.8
Asia	59.2	52.6	65.1	69.7	68.0	70.9
Oceania	47.8	46.9	48.5	65.6	62.6	68.1
Nothern America	37.9	32.2	42.8	49.3	44.0	54.1
Europe	21.0	14.1	27.1	29.2	23.4	33.9

GEOGRAPHICAL CANCER REASONS

Some regions and countries in **Table III** differ significantly in the prevalence of specific types of cancer. For instance, stomach cancer in Eastern Asia; cervix uteri in Malawi/Eastern Africa; bladder in Europe; non-melanoma of skin in Australia/New Zealand; Kaposi sarcoma in Africa; lip and oral cavity in Papua New Guinea/Melanesia. Each of these similarities can be attributed to specific reasons. For example, Eastern Asia accounts for more than half of all stomach-gastric cancer cases[17], and it is related to high rates of infection with *Helicobacter pylori* and the increased consumption of salted and smoked foods[18]. The highest cervical cancer rates in Malawi/Eastern Africa are coordinated with a high prevalence of human immunodeficiency virus (HIV) with 10.6% and human papillomavirus (HPV) with 33.6%. Late diagnosis and limited cancer treatment options also increase the incidence of this disease[19].

Smoking is shown as the most critical cause of bladder cancer. This cancer type is most common in Europe[20]. Furthermore, given the high and growing smoking levels in Europe, we can say that this trend is expected. Even Greece has the highest smoking rate in Europe at 42%, and it is no coincidence that Greece ranks first in the world incidence and makes Southern Europa the world's largest region in this incidence[21].

The prevalence of skin non-melanoma in Australia/New Zealand is mainly due to the region's geographical location. Thus, it is considered that this cancer type in Australia/New Zealand is caused by exposure to UV radiation in sunlight. It should be noted that the incidence and mortality of this disease in this region differ sharply from other areas[22,23].

A virus called human herpesvirus, also known as Kaposi sarcoma-associated herpesvirus (KSHV), high-rated in Africa, is the cause of Kaposi sarcoma. Medical specialists believe that the virus is primarily transmitted from mother to kid through saliva. The malignancy develops in the context of a reduction in immune function, even if humans have carried the virus their entire lives[24]. Endemic Kaposi's sarcoma in Africa is also associated with geographical causes. The proximity of the regions where the disease is most prevalent to areas rich in volcanic clay minerals, the high incidence on the feet and legs, and the predominance of rural peasants and cultivators indicate the same etiology[25].

The most common oral cancer in Papua New Guinea is undoubtedly due to their traditional habit. This routine is associated with the Areca palm (*Areca catechu*) seed, called betel nut, and 80% of the country's population, even children, often chew this plant throughout the day. It is important to note that this plant has psychoactive properties, and the possibility of the population's dependence on it is a logical approach. For years, this ancient custom has ranked Papua New Guinea as the leading cause of oral cancer incidence and mortality[26,27].

PEGANUM HARMALA ALKALOIDS AGAINST CANCER CELLS

Most drugs used to treat cancer contain chemicals. However, given the current medical and social challenges in treatment and the predictions that cancer will be more prevalent in the future, there is a greater need for more readily available,

effective sources. In this case, attention is focused on plants[28]. One of such herbal substances used in modern practice is vincristine. It is derived from *Catharanthus roseus* and is used against cancer under the name Oncovin. Lymphoid blast crisis of chronic myeloid leukemia, acute lymphocytic leukemia, and Hodgkin and Non-Hodgkin lymphoma are the indications for vincristine approved by the US Food and Drug Administration (FDA)[29].

Peganum harmala (**Figure 1**) is one of the potential plants whose treatment area can be developed and expanded in the cancer problem. For example, Spinal-Z, medicament in the capsule form of methanolic extract of *P. harmala* seeds and *Dracocephalum kotschyi* leaves, is used for gastric cancer treatment in Iran[30]. According to the literature, this medicine can reduce the viability of cancer cell lines in mice[31].

Figure 1. *Peganum harmala* fruit and seeds[12]

Peganum harmala is a plant rich in amino acids[32], minerals[33], and lipids[34]. However, this plant is especially famous for its alkaloid content. The most frequently encountered alkaloids, quantitatively and qualitatively, are harmine, harmaline, harmol, and harmalol[35,36]. These compounds are in the researchers' focus with their anticancer effects. The antitumor properties of these alkaloids against various cancer cells have been studied, high results have been obtained, and research in this area is ongoing. The effects of Peganum alkaloids on many cancer cells have not been researched, meaning that some gaps and areas need to be investigated. **Table IV** shows this deficiency also cancer and cell types in which the effects of these alkaloids have been studied so far.

Table IV. Anticancer studies on *P. harmala* alkaloids

Types of cancer and cell lines	References			
	Harmine	**Harmaline**	**Harmol**	**Harmalol**
Breast; mammary gland				
MDA-MB-231	**11,37,38,39,40,41**	**11**	-	**42,43**
MCF-7	**11,37,41,44,45,46,47,48,49,50**	**11,48,50**	-	-
BT549	**51**	-	-	-
BCaP-37	-	**50**	-	-
4T1 (mouse)	**51**	-	-	-
Thyroid				
TPC-1	**52**	-	-	-
Large intestine; colon				
HCT116	**44,49**	-	-	-
SW480	**53**	-	-	-
SW620	**54**	-	-	-
LoVo	-	**50**	-	-
Stomach (gastric)				
SGC-7901	**55,56**	**57**	-	-
SGC-790	**53**	-	-	-
MGC-803	**56,58**	-	-	-
BGC-823	**53**	**50**	-	-
Brain				
U87	**59**	**59**	**59**	**59**
H4	**59**	**59**	**59**	**59**
U373	**60**	-	-	-
T98G	**60**	-	-	-
Hs683	**39,60**	-	-	-
GBM	**61**	-	-	-

U251MG	-	-	**39**	-
Oesophagus				
OE21	**60**	-	-	-
OE33	**60**	-	-	-
ESCC	-	**62**	-	-
Pancreas				
PANC-1	**63**	-	-	-
CFPAC-1	**63**	-	-	-
SW-1990	**63**	-	-	-
BxPC-3	**63**	-	-	-
Lung				
LLC (mouse)	**50,64**	-	-	-
CCD18LU (normal)	**53**	-	-	-
A549	-	**65**	**66**	**42,43**
H596	-	-	**67**	-
H1299	-	**65**	-	-
Liver				
HepG2	**46,50,64,68**	-	-	**42,43,50,69**
L02	**46**	-	-	-
Hep3B	**50**	**50**	-	-
WRL-68	-	-	-	**42**
SMMC-7721	**58**	-	-	-
HepA (mouse)	**64**	-	-	-
Hepa 1c1c7 (mouse)	-	-	-	**50**
Uterus; cervix				
HeLa	**50,53**	**50**	-	**42,43**
HEp-2 (HeLa derivative)	-	**50**	-	-
C-33A	**53**	-	-	-
Ovary				
OVCAR-3	**49**	-	-	-
Peripheral blood (leukemia)				
HL-60	**50,53,70**	**50,70**	-	-
Jurkat, Clone E6-1	**71**	-	-	-
Bone; marrow (leukemia)				
K562	**50,53**	**50**	-	-
Umbilical vein				
HUVEC	**57**	-	-	-
Urinary bladder				
RT112	**57**	-	-	-
RT4	**57**	-	-	-
SW780	**53,72**	-	-	-
BIU87	**72**	-	-	-
5637	**72**	-	-	-
Ureter; uroepithelium				
SV-HUC-1 (normal cell)	**72**	-	-	-
Skin				
SKMEL-28	**39**	-	-	-
UACC-62	**48,50**	**48,50**	-	-
B16F-10 (mouse)	**50,73**	-	-	-
L1210 (mouse)	-	**50**	-	-
Kidney				
TK10	**48,50**	**48,50**	-	-
Spleen				
Sp2/O-Ag14	**50,71**	-	-	-
Hemo-lymphocytic				
P388 (mouse)	-	**50**	-	-
B lymphocyte				
Raji	-	**50**	-	-
Muscle				
RD	-	**50**	-	-
Sarcoma				
S180	**50,64**	**50**	-	-
UCP-med (rat)	**71**	-	-	-
L2 reticulosarcoma (rat)	-	**71**	-	-
Carcinoma				
Med-mek (rat)	**71**	-	-	-
UCP-med (rat)	**71**	-	-	-

CONCLUSION

Given current cancer rates and future prognoses, there is a need for alternative compounds that are easier to find. In this case, the first thing that comes to mind is plants, and one of the most important plants in this area is *P. harmala*. In this article, the potential for cancer treatment through experiments with this plant and its essential alkaloids and scientific gaps have been shown.

ACKNOWLEDGMENT

The author received no financial support for the review, authorship, or publication of this article.

AUTHORS' CONTRIBUTION

Tohfa Nasibova performed the entire role of this review.

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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