A classical approach on Artemisinin: The Chinese wonder drug

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Abstract

Cancer and Malaria are the two serious disease that has been the biggest challenges of the century. The issue of climate change and global warming has worsened the problems to many folds. However, the pandemic of COVID-19 has added woes to the reeling problem of these two disease and hasten the mortality rate of human population to a greater number. Some of the shortcomings of presently used drugs are poor solubility and toxicity. Therefore, an innovative and integrative approach is required to overcome the above said limitations of drugs. Artemisinin based compound therapies (ACT) can be one of the promising treatment for all the problems as a potent factor of herbal remedies in curing the disease. ACT combines Artemisinin derivatives (ATRs) with a distinct group of drugs for their action. This process is more efficient and act faster than any other one. Artemisinin obtained from *Artemisinin annua* was first discovered for malaria and later on its was found suitable for cancer and Covid -19 making it a wonder drug. In this review we tried to redefine the role of Artemisinin with a particular emphasis on its anti-malaria, neoplastic activity and COVID-19. We have adopted a pragmatic approach to include the mechanism by which it act and its role in future for treating the diseases which has cause high morbidity in human population.

Key words: Cancer, Malaria, ACT, ATRs, Artemisinin, COVID-19

1. Introduction

The case of malaria is on rise globally and this has caused a negative impact on the socio-economic conditions of the community enhancing a lot of finance and health burden associated with it (Peter et al.2021). According to WHO study, there are 247 million cases in 2021, up from 245 million cases in 2020 (WHO,2022). The causal organisms are five Protozoan parasites: P. falciparum, P. vivax, P. Ovale, P. malariae and P. knowlesii. Among them P. falciparum is most deadly (Antinori et al. 2012). Malaria is a life threatening disease mostly prevalent in tropics and sub-tropical as one of the major epidemics. Over the decades there has been a constant effort by WHO to reduce the cases of malaria in Asian and African sub continents. Since 2015, nine countries belonging to these sub continents have been certified as completely free from malaria. In other countries a massive effort by WHO and different government agencies to eradicate and eliminate malaria. A lot of preventive strategies has been designed and developed by the researchers over the years to combat the disease. However, a lot of challenges has been met for evaluating the efficacy of a drug in eliminating malaria. The cardinal point while following the evaluation procedure has been the behavior of human being and the strains of the vector. With advent of drugs like chloroquine, mefloquine, and quinine there is a great success in diminishing the number of affected persons from 77% to 48% over 100 years. In recent years, drug resilience has been one of the major backlog for treatment. Another disease which has cause a great carnage of human population is cancer (Li J and Zhou 2010).

Cancer is one of the greatest maladies of recent times. It accounts for nearly 10 million deaths in 2020. 13% of cancer diagnosed in 2018 due to viral infection such as human immune defiency virus, hepatitis C virus and human papilloma virus. In the present times drugs used in cancer suffers from toxicity and target specific (Li and Zhou 2010).

One of the greatest pandemics that has engulfed the world in 2020 was SARs-COV-2 and has caused enormous number of morbidity (Agrawal et al.2022)

The finding of Artemisinin from *Artemisinin annua* (Chinese worn wood) has been one of the greatest discoveries of Chinese Scientist so far. Artemisinin has a prolong history to be used as Quinghasou in traditional Chinese treatment (Su et al 2015) This wonder drug has been panacea for treating almost all deadly disease. ACT (Artemisinin Combinational Therapy) and ARTs (Artemisinin and its derivatives) has become one of the promising treatments for all the above-mentioned disease.

Artemisinin (and its various derivatives, which is collectively as "Artemisinin") is a Sesquiterpene lactones (Wang et al 2019). Which contain a peroxide bridge unique to it. Artemisinin combination Therapy (ACT) is one of the most effective treatments available for many diseases. The endoperoxide bridge exhibiting its activity, is clearly observed in cancer, malaria and Covid. ACT efficacy depends upon ARTs (Artemisinin and its derivatives) action.

The combination of Artemisinin with other bioactive agents is one potent strategy to overcome the challenges faced by known anticancer and antimalarial drugs. Artemisinin is one of the drug used for primary treatment of malaria. It is also prominent in the medicinal industry because it exhibits a wide range of biological activities including antimalarial, antifungal, anticancer, anti-HIV, antibacterial and antiviral etc (O'Neill et al.2010).

If we compare the anti-malaria activity of Artemisinin and Cinchona phytoextracts. ARTs (Artemisinin and its derivatives) will always gain an upper hand as it kills both asexual and sexual stage. Whereas Quinone activity is limited to one stage (Sato 2021). In recent time, a lot of strategy has been developed to garner strength against the protozoan parasite like preventive chemotherapy, vaccination and vector control stills there lays of difficulties in implementing them as lot of problem has aroused like drug resistance and virulence have risen. In the present scenario Artemisinin shows a promising results. However, its activity is limited by short half-life period and its solubility.

In this review, we provide an overview of the potent efficacy of Artemisinin in the treatment of cancer malaria and SARs-Covid. The mechanism of action of the drug concerning this disease and its relevance in the near future has been elaborately discussed. Also in the current study we have schematically described the metabolic synthesis of Artemisinin and illuminating the mode of its actions in different disease such as Malaria, Cancer and Covid. This review have to tried the justify the role of Artemisinin and its derivatives, the active principle of the plant *Artemisia annua* used in indigenous Chinese treatment for ameliorating various maladies and have to repurpose the role of it in the present Covid-19 era.

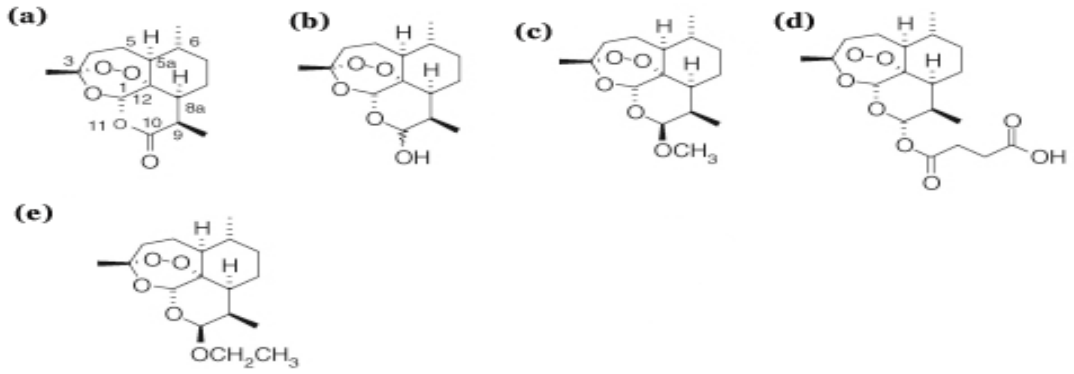

Figure 1: Artemisinin and its derivatives. Artemisinin (a) isolated in crystalline form in 1973 from Artemisia annua and derivatives dihydroArtemisinin (DHA) (b), artemether (c), artesunate (d) and Artemisone (e).

2. Metabolic Engineering:

Artemisinin biosynthesis is a major benefit of metabolic engineering is that it allows for the introduction of novel metabolic pathways into organisms that do not already have them. To introduce the metabolic pathway, a detailed understanding of that pathway must first be developed. As far as Artemisinin's biosynthesis pathway is concerned, it has almost "solidified". A crucial link between the Mevalonate route (MEV) and terpene biosynthesis, Farnesly diphosphate (FPP), is the precursor to Artemisinin. In order for FPP to form, HMGR and Faresyl pyrophosphate/Diphosphate synthese (FPS/DPS) must function. This is because HMGR is the only enzyme capable of catalyzing the HMG-CoA to mevalonate conversion, which is the first step in the mevalonate pathway. This makes HMGR the rate-limiting enzyme of the MEV pathway, as it controls the rate of all other steps in the pathway. A substance called IPP is mainly found in cytosol (MEV) and plastid (MEP) by means of the substrates used to catalyze the FPS reaction of IPP and DMAP. CYP17AV1 is the first enzyme in the pathway to convert the volatile into its active form. It is then converted to AAOH (alcohol) by CYP71AV1 and then further to AAA (Artemisinin aldehyde) by ADS. As a result of the reduction of AAA by Dbr2 (Artemisinin aldehyde double bond reductase), dihydroartemisinic aldehyde (DHAAA) is generated, which converted to DHAA (dihydroartemisinic) by oxidized aldh1. Non enzymatic and most likely spontaneous photo-oxidation processes are involved in the following conversions of DHA to Artemisinin and AA to Artemisinin Figure 2. Terpene transport plays a crucial role in the buildup of

the precursors. However, it's crucial to show how AA and DHAA collect in secretory cells before they migrate to the apoplastic space. Pathway engineering may benefit from greater research into the underlying transport processes of Artemisinin precursors (Tyagi et al 2018) (Sirivibulkovit et al 2018) (Tang K, Shen et al 2014).

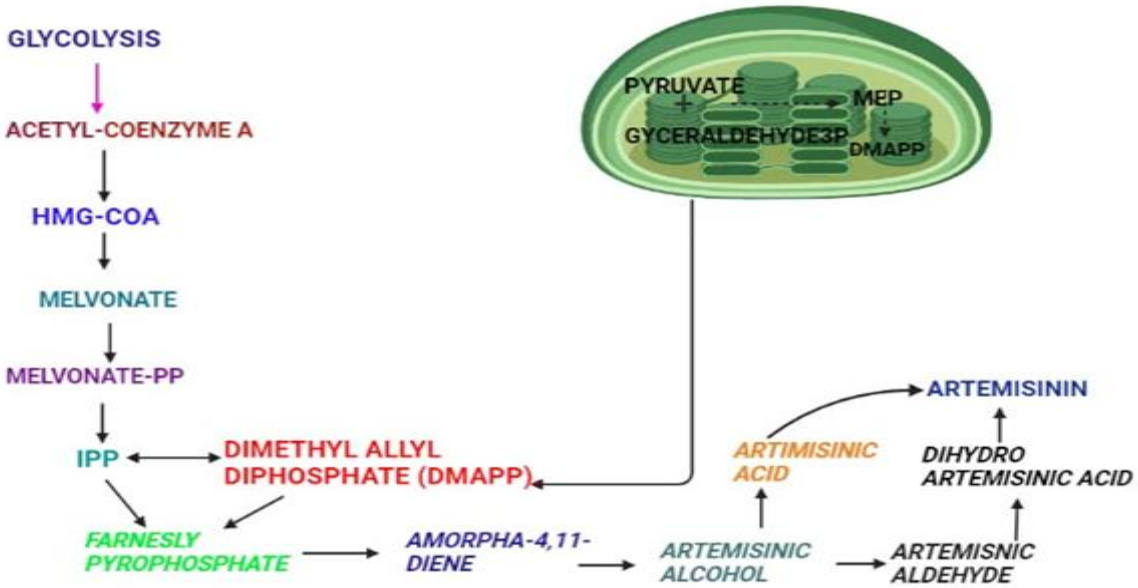

Figure 2: Skeletal Mechanisms of Metabolic Pathway in Arteminin

2.1 Mechanisms of Action:

There is a perplexed view regarding the potential activity of Artemisinin, however it is clearly understood that the presence of the endoperoxide bridge is responsible for all its pharmacological activity Figure 3.

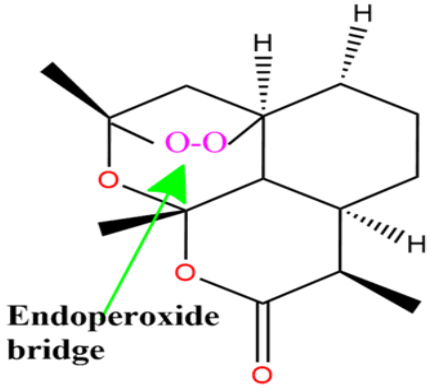

Figure 3: Structure of Artemisinin with its Endoperoxide bridge.

3. Artemisinin and Malaria.

Malaria parasites feed on the host's haemoglobin as part of their life cycle. Haemoglobin is transported into the acidic food vacuole and degraded to aa by proteolytic enzymes termed plasmepsins. An amount of four equivalents of heme (ferroprotoporphyrin IX) is released, which leads hematin, a toxic to microorganisms in free state. However, the parasite develops mechanisms convert the hematin to hemozoin, which is nontoxic. However ferrous ion (Fe2+) from heme brings about a cleavage in the endoperoxide bridge which results in the formation of $ROS^{\cdot}$ And rearranges themselves to form stable carbon radicals. These free Artemisinin-radicals are important for the antimalarial activity of the parasite (Xie et al.2016) (Susan et al 1996) (Haynes et al.2013) (Table1, Fig.-3)

3.1 Mechanistic Insights:

Heme/Fe^{2+}

Posner and Jefford have well illustrated the oxidative stress induced by free radical mechanisms by heme/Fe^{2+}. (Posner and Oh 1992) (Posner et al.1994) (Jefford et al.1995).

The initial opening of the peroxide bridge is driven by heme Fe (II) or an additional source of ferrous ion to any radicals, which then restructures into either of two carbon-centered species. The reaction of Fe(II) with oxygen 1 produces an hydroxyl radical, results in the formation of a main carbon-centered radical(Haynes et al.2013)(O'Neill and Bard 2010). Conversely, interaction with oxygen2 produces oxy radical species capable of producing secondary centered radicals. Malaria parasites dies as a result of the ultimate alkylation of macromolecules such as heme, certain proteins, and other targets.

Peroxide

An alternative view of the ring opening is by the promotion of the peroxide. A heterolytic breakdown of the endoperoxide bridge results in the release of H_2O (nucleophile) once the unsaturated hydroperoxide is created (O'Neill and Bard 2010). In response to this fenton –like degradation, H_2O_2 is produced, releasing OH, in addition, an alternative pathway can also produce a variety of reactive oxygen species (ROS) that are equally relevant for antimicrobial activities. The study led by Haynes

and co-workers demonstrated that Artemisinin promotes N- oxidation via its extended peroxyl form. Based on the heme model, Artemisinin is believed to inhibit malaria by acting inside the vacuoles, by cleaving heme, free radicals generated by Artemisinin will arbitrarily alkalyte nearby vacuoles. To be successful, the Artemisinin model needs a protein target that is specifically connected to Artemisinin. It will assist in understanding Artemisinin's chirality (O'Neill and Posner 2004). Chiraliry also may not affect heme-Artemisinin interactions. Originally, it was recommended that activated Artemisinin could target heme. Like chloroquine, Artemisinin blocks the removal of heme from the blood in vacuoles to prevent malaria. (Li and Zhou 2010).

PfATP6

A structural comparison of Artemisinin with thapsigargin demonstrated that it is particularly effective at binding and inhibiting the sarcoplasmic/endoplasmic calcium ATPase (SERCA) without an endoperoxide link. To investigate the role that this interaction plays in the killing of P. falciparum malaria by Artemisinin and SERCA (Wicht et al.2020). Although both Artemisinin and thapsigargin are powerful inhibitors of PfATP6, it is a curious finding that thapsigargin counteracted artimisinin's antimalarial action. A strong link was also discovered between Artemisinin and several of its derivatives opposed to PfATP6 and their capacity to eradicate cultured parasites (Pulcini et al.2013). It was found that fluorescent thapsigargin derivatives did not label parasites after preincubation with Artemisinin, demonstrating that it targets the same area as thapsigargin (Ismail et al.2016).

Mitochondria

Based on mitochondrial model, Artemisinins could hinder mitochondrial processes by producing ROS, a nonspecific hazardous agent, rather than inactivating a specific protein target. Because Artemisinin has no impact on mammalian cells, it is hypothesized that the special action is owing to Artemisinin yeast and malaria activation; nevertheless, mammalian mitochondria may be unable to bring about the drug's action (Moore et al 2022).

3.2 Artemisinins and its Antimalarial Activities.

Although, many steps have been introduced for treating the malaria. However, the small organic molecules of plants such as Cinchona, Artemisinin, diterpenes and phytol drive an essential role in eradicating malaria. These phyto extracts are harmoniously used in induction therapy or primary treatment. This has been well illustrated in Table.1

Table 1: Showing Secondary Metabolites and their anti-malaria activity.

Sl no.	Mosquito type	Metabolites	Activity	References
1	Plasmodium falciparum	Chinchona (alkanoids and qinghaosu)	Antimalarial pharmacopeia	Warrell 1990
2	Plasmodium falciparum	Eupatorine, Isovitexin, Luteolin	Chloroquine insensitive (FCR3, 7G8, Dd2, K1, and FCR3) and Chloroquine sensitive (HB3 and 3D7) act against antimalarial activity	S. JO et al. 2013
3	TM4 (P. falciparum)	Miusacunines A(9)	Compound 9 inhibited the action of the TM4 Malaria stain	Promchai et al., 2016
4	D6 and W2 (Plasmodium falciparum)	Polysporin (1) and rhaphidecurperoxin (2)	Antimalaria activities against D6 and W2 atrain	Zhang et al. 2001
5	D10 (P. falciparum	2-isopropenyl-6-acetyl1-8-methoxy-1,3-benzodioxin-4-one	Antimalarial activity against D10	Chung et al. 2010
6	PoW and Dd2 (P. falciparum)	Diterpenes, E-Phytol (20) (Pow) and 6E-geranylgeraniol-19-oic acid (21)	Active compounds against malaria	Angupale et al. 2013
7	Plasmodium berghei	Acetylenicthiophenes, 5-(pentta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (22)	contain antimalarial activities	
8	HB3 (P. falciparum)	Lupine triterpenes (24-31), 23-0-(trans)-feruloyl-23-hydroxybetulin compound from Buxus sempervirens plant	Antimalarial activities	Cai et al. 2016
9	P. falciparum	Tormentic acid	P. falciparum chloroquine resistant parasites (W2)are inhibited.	Uchoa et al. 2010
10	FCR-3 (P. falciparum)	Three kaurene diterpene lactones	FCR-3 specific antimalarial activities	Uys et al. 2002
11	K1 (P. falciparum)	9-0-demethyltrigonostemone (87) and a new phenanthropolone, 3, 6, 9-trimethoxyphenanthropolone	Antimalarial effectiveness against the multiresistant K1 strain of Plasmodium falciparum	Seephonkai et al. 2009
12	FcB1 (P . falciparum)	(+)-catechin 5-gallate and (+)-catechin 3-gallate	Antimalarial activity opposed to FcB1 strain	Ramanandraibe et al. 2009
13	D6 and W2 (P. falciparum)	Prosopilosidine and isoprosopilosidine	Antimalarial activity against D6 and W2 strains	Samoylenko et al. 2009
14	W2 (P. falciparum)	3-geranyloxyemodin anthrone	Antimalarial activity against W2 strain	Lenta et al. 2008
15	K1 (P. falciparum)	Luteolin 7-O-β-D- glucopyranoside	Antimalarial constituents and show activity against K1 clones	Kirmizibekmez et al. 2004
16	NF-54 (P. falciparum)	4-hydroxy-α-tetralone and tetralone-4-O-β-D-glucopyranoside	Antimalarial activity against NF-54 strain	Upadhyay et al. 2014
17	P. falciparum	Two Alkaloids,5-hydroxynoracronycine	Antimalarial activity	Lacroix et al. 2011
18	W2/D6 (P. falciparum)	Eurycomanone and pasakbumin B	Antimalarial activities against W2/D6 strain	Kuo et al. 2004
19	K1 (P. falciparum)	Quassinoid neosergeolide , the indole	Contain inhibitory	De Andrade et al.

		alkaloids ellipticine, aspidocarpine, and 4-nerolidylcatechol	activity against the k1 strain and these compounds with antimalarial property greater than quinine and chloroquine.	2007
20	D6/W2 (P. falciparum)	3α,20-lupandiol, 2α, 3β-dihydroxyolean-12-en-28-oic acid, and 2,6-dimethoxy-1- acetonylquinol	Antimalaria activity against D6 and W2 clones.	Zhang et al. 2006
21	D10 (P. falciparum)	α-pyrone, Lippi lactone	Active against the D 10 strain contain antimalaria activity. Compound 119 is also mildly cytotoxic.	Ludere et al. 2013
22	P. falciparum	α-pyrone, Lippi lactone	Antiplasmodial activity against P. falciparum	Jansen et al. 2017
23	3D7 (P. falciparum)	Phenolic compound	Antimalarial activity on P. falciparum due to high phenolic content.	Kang et al. 2014

4. Artemisinins as a novel Anti-Cancer therapy.

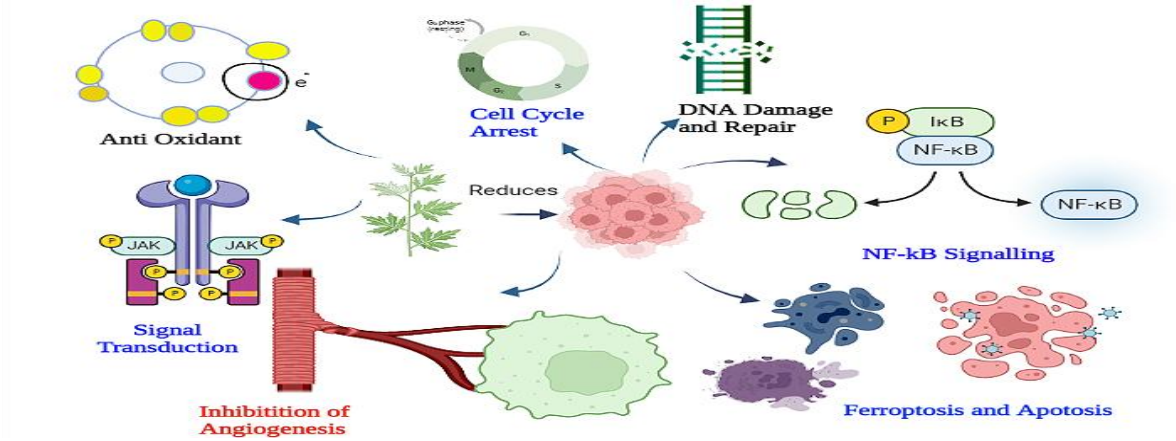

Figure 4: A perspective on mechanisms of Artemisinin on cancer.

4.1 Mechanism

Artemisinin promotes cell damage by creating oxygen free radicals such as hydroxyl and superoxide anion radicals, a features shared by all neoplastic medicines. When exposed to free iron, Artemisinin is transformed into radicals of alkyl capable of causing direct oxidative damage in cancer cells. As they are more susceptible to the ROS species due to low levels of antioxidant enzymes in tumor cells

(Wondrak 2009). Artemisinin and its derivatives have greater potency in anticancer activity then Artemisinin alone. Apoptosis is the best plausible mechanism by which the anticancer activity of Artemisin is manifested. Programmed cell death is caused by the up regulation of tumor suppressor protein TP53 which lead to improve the level of proapoptotic protein and cytochrome C (caspase activator). A balance between pro (BAX, BAK, BAD, Bid) and apoptotic protein (Bcl-2 and Bcl-xl) are intrinsic for apoptosis and cell death. Apoptosis can be induced by Artemisinin by activating BAX directly in lung and prostate cancer cell lines (Isani et al.2019). Apart from mitochondrial apoptosis, Artesunate can induce apoptosis by producing Cytochrome C and procaspases-2,3, in breast cancer cell line and leukemia -T cells via Fe^{2+}/Fe^{3+} dependent oxidant (Zhang et al.2017). Artesunate has played a major role in decreasing colon cancer by impeding the biosynthetic pathway of fatty acid pathway and the NF-β pathway (Augustin et al.2020). According to researchers, Artemisinin exhibit cell cycle arrest in a variety of ways. Artemisinin aptly act in cell cycle arrest by setting of G1phase cyclins which arrest the neoplastic growth in breast and oropharyngeal cancer (Sun et al.2019). Artesunate triggers the cell cycle arrest at G2/M phase and cell death in renal cell carcinoma (Chen et al. 2014). The levels of cyclin B, cyclin D1 and the transcription factor E2F1 were also detected to be regulated by Artemisinin in. Artemisinin increased the expression of p16 and p27 while suppressing cyclin D1, Cyclin E, CDK2, CDK and CDK6 in adult nasopharyngeal cancer cells (Song et al.2015). Furthermore, Artemisinins block the transcription of the cyclin CDK promotor in prostate cancer cells by inactivating the retinoblastoma protein (pRb), a mediator of cell cycle progression (Wu et al.2011). DHA has been found to inhibit cell cycle progression. The downregulation of CDK2, CDK6, and cyclinE, as well as NF-β, induces the transition of pancreatic cell lines from G0/G1 to S phase. The levels of P27 inhibitory protein were increased (Augustin et al 2020). Artesunate advocated apoptosis and arrest of G2/ M in cervical cancer line (Kiani et al.2020).

4.2 Anticancer activities of Artemisinin.

In a nutshell, the anti-tumor activity of ARTs mainly occurs by apoptosis in Cancer. ROS and carbon free radical plays a major role in it. Although apoptosis has a major chunk for antineoplastic activity, other processes such as oncosis, autophagy and ferroptosis which is elaborated in Table 2.

Table 2: Showing the mode of action of Artemisinin in cancer.

Sl no.	Cancer Type	Cell Line	Mechanism	References
1	Hepatocellular Carcinoma	HepG2	Arrest the cell cycle in the G1 phase	Hou et al. 2008
		Hep3B	More Kip1/p27 and Cip1/p21 being produced	
2	Neuroblastoma	UKF-NB-3	Activate caspase -3 to trigger apoptosis	Paprocki et al. 2010
3	Ovarian Cancer	OVCA-420	In a dose and time dependent manner, Inhibit cell proliferation	Jiao et al. 2007
		OVCA-439	Target the Bcl-2 family to cause apoptosis	
		OVCA-433	Reduce the antiapoptotic protein Bcl-xLand and Bcl-2 expression	
4	Breast Cancer	MDAMB-453	Improve the time and dose- dependent resistance of the cancer cells to ferroptosis	Yao et al. 2018
		MCF7	The cytotoxicity of cancer cells is reduced by 3-caffeoy lquinic acid (3CA)	Chen et al. 2020
5	Pancreatic Cancer	BxPC-3	Cell cycle arrest in G0/G1	Chen et al. 2010
		PANC-1	Reduce NF-B activity and the expression of IL-8, MMP-9, VEGF, and COX-2	Wang et al. 2011
6	Lung Cancer	A549	Cause apoptosis	K. Liao et al. 2014
7	Pancreatic Cancer	BxPc3-RFP	Inhibits the growth of new cells triggers apoptosis	Aung et al. 2011
8	Colon Cancer	HCT116 HT29	Increase of ROS and g-H2AX	Frohlich et al. 2017
9	Epithelioid Sarcoma	PANC-1 CFPAC-1	Prevent cell development, trigger apoptosis, and activate HSP 20 and HSP 27	Liu et al. 2013
10	Hepatocellular Carcinoma	HepG2 SNU-182 SNU-449	Bring about ferroptosis	Li et al. 2021
11	Cervical Cancer	HeLa SiHa	Give rise to cytotoxicity influence necrosis in HeLa and apoptosis	Zhu et al. 2014
12	Neuroblastoma	UKF-NB-3	Caspase-3 activation will cause apoptosis.	Paprocki et al., 2010
13	Osteosarcoma	HOS	Cell cycle arrest at G2/M phase cause by ART and trigger apoptosis.	Q. Xu et al, 2011
14	Melanoma	SK-Mel-28	Cause apoptosis	Steinbruck et al. 2010
15	Myeloid Leukemia	AML cell lines	Creat the first regression	Drenberg et al., 2016
16	Nasopharyngeal Cancer	CNE-2 cells	G1 phase of the cell cycle arrest and inhibition of invasion, colony formation, and cell motility	Huang et al. 2016
17	Human Fibrosarcoma	HT-1080 Cells	MMP-9 expression is reduced.	Hwang et al. 2010
18	Liver Cancer	A549 MCF-7 HepG-2 MDA-MB-231	At G2 phase, the cell cycle is arrested.	Hu et al. 2019

19	Endomaterial Cancer	Ishikawa cells	Caused the arrest of the G1 cell cycle and downregulated the mRNA and protein levels of CDK2 and CDK4.	Tran et al. 2014
20	Kaposi's Sarcoma	KS-IMM	Activate apoptosis and inhibit angiogenesis	Dell'Eva et al. 2004,
21	Oral Cancer	Human gingival epithelial (IHGK) cells	In cell cycle S- phase rate increase. Through apoptosis, AR kills altered oral epithelial cells.	yamachika et al. 2004
22	Skin Cancer	A431 (Human epidermoid carcinoma cells)	Arrest of cell cycle at G0/G1 phase occur due to downregulation by RTcan different cyclins.	Zhongyang et al. 2012
23	Thyroid Cancer	GSJO cell line	Induce apoptosis	Rinner et al. 2004
24	Gastric Cancer	PG100	Induced apoptosis	Alcantara et al., 2013
25	Brain Cancer	C6 Glioma cells	Triggering antiangiogenesis. Tumor development was inhibited by artemether	Wu et al. 2009
26	Metastatic prostate Cancer	LNCap (Androgen-responsive PCa Cells)	Apoptosis through the downregulation and activate caspase-3	Nunes et al. 2017
27	Non-small-cell lung cancer	NSCLC cell	VE-Cad, TGF-b1, MMP-2, and HIF1a levels should be downregulated	Liu et al. 2019,
28	Leukimia	CCRF-CEM	Higher cytotoxicity compared to doxorubicin	Frohlich et al, 2017
29	Pulmonary Metastasis	B16F10	Decrease form of metastatic nodules	Conesa et al. 2005

SARS-COV-19

Artemisinin derived Artesunate has been considered the front line treatment severe types of malaria. The antineoplasticity effect of artesunate has been recorded for many cancers, importantly, artesunate has antiviral effects against DNA and RNA viruses. Accordingly, artesunate can decrease the risk of death from SARS- CoV- 2 infection, Uzun and Topas proposed artesunate as an anti- COVID- 19 agent because of the modulatory effect on inflammation and chloroquine- like endocytosis(Uzun and Toptas 2020) (Shi et al.2022).

Mechanism

Artesunate carried the highest anti-SARS-CoV-2 activity, followed by artemethe. *A.annua* extracts and Artemisinin are effective as anti-viral for COVID-19 management. (Agrawal et al.2022)

"Cytokine storm" contributes to the death rate caused by COVID-19. Artemisin act by controlling the immune system which impedes the cytokine release such as IL-6, IL1β, and TNF-α. Thus reducing the infection and the mortality rate. Cytokine Storm in COVID-19: The Current Evidence and Treatment

Strategies (Tang et al.2020) A combination of Artemisinin-based medicines (dihydroArtemisinin-piperaquine, artemether- lumefantrine, artesunate-amodiaquine and artesunate-mefloquine) is recommended by the world Health Organization (WHO) for the treatment of malaria. Mefloquine-artesunate showed the highest inhibitory rate among these four ACTs in vitro for treating COVID-19. A clinical trial found that Artemisinin-piperaquine effectively reduced the average time to undetectable virus RNA. As a result, Artemisinin and its derivatives may be utilised as an alternate treatment for COVID-19. Extracts from *A. annua* such as Artemisinin, artesunate and artemether can attack SARS-COV-2 (Tang et al.2020) The intrinsic approach is based on interaction with a spike glycoprotein which has been well observed in VeroE6 cells (Amani et al.2022) (Gendrot et al.2020).

5. Conclusion and Future Perspective.

Artemisinin derived from *Artemisinin annua* has been firmly established as one of the effective drug molecule for malaria. Approval and current medical use of it in ACT for first line treatment of malaria confirms its efficacy. In addition to this the Artemisinin and its dervatives have stood out as good pharmacophore for treatment of cancer. The drug is active against parasites such as *Schistomosa*, *Leishmania* and *Toxaplasma*. Several hybrid compounds incorporating Artemisinin scaffolds have been reported as potential new, affordable, and effective therapeutic agents for the treatment of other disease like hepatitisis B, C, HIV-1 and also exhibit antifungal activity. In both malaria and tumor cells, the primary source of activator is an iron, which is well supported by strong evidences. The iron may be in the form of Fe2+ or heme. Which widens its area of activity and opens new areas to explore. Artemisinin has been limited for its life span and bioavailability. It has been investigated to use innovative design approaches that include hybrid medications and the finding of chemically and metabolically stable Artemisinin derivatives. Artemisinin's as a drug have diverse multifaceted biological properties including strong anticancer activity. This drug is more economical and poses the ability to face the challenges of advanced cancer. Affiliation of this drug with multiple mechanism which include ROS (Reactive oxygen species), apoptosis, oxidative DNA damage and sustain DNA double strand break, in antitumor activity still now not properly investigated. Which could be widely explored in near future, so that a novel drug could be designed synthetically in preventing both the deadly disease of cancer and malaria. More search for novel, cost-effective and therapeutic agents with improved efficacy for the treatment of cancer, malaria and Covid has resulted in the reports of several hybrid compounds containing Artemisinin scaffolds.

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