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Review

Anti-malarials are anti-cancers and *vice versa* – One arrow two sparrows

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ABSTRACT

Repurposing is the novel means of drug discovery in modern science due to its affordability, safety and availability. Here, we systematically discussed the efficacy and mode of action of multiple bioactive, synthetic compounds and their potential derivatives which are used to treat/prevent malaria and cancer. We have also discussed the detailed molecular pathway involved in anti-cancer potentiality of an anti-malarial drug and *vice versa.* Although the causative agents, pathophysiology and manifestation of both the diseases are different but special emphasis has been given on similar pathways governing disease manifestation and the drugs which act through deregulating those pathways. Finally, a future direction has been speculated to combat these two diseases by a single agent developed using nanotechnology. Extended combination and new formulation of existing drugs for one disease may lead to the discovery of drug for other diseases like an arrow for two sparrows.

Contents

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1. Introduction

The repurposing or switching of therapeutic target is the novel means of drug discovery in modern pharmaceutical science. A significant advantage of drug repositioning over the traditional drug development is its safety, cost-effectivity and easy availability in the market. The repositioned drug has already passed a significant series of toxicity and other tests as well as clinical trial before being introduced in the market thus several toxicity issues will be omitted for further use in other purposes. There are multiple examples of successful repurposing approach in the field of drug discovery. For instance, sildenafil (Viagra) was initially used for cardiac disorders but now used for erectile dysfunction treatment. Colesevelam was originally developed to reduce elevated LDL cholesterol but now employed for type 2 diabetes mellitus treatment (Fonseca et al., 2008). Gabapectin originally used for epilepsy is now a routine medicine for anxiety treatment (Attal et al., 2010).

Cancer is a deadly disease where cells divide in an uncontrolled manner and it can develop in any part of the body in any form such as liquid, solid, *etc.* (Sung et al., 2011). It is the leading cause of death across the globe. Failure to control the disease emerges as one of the most prominent reasons for its lethality. Despite the availability of a number of conventional therapies ranging from surgery, radiotherapy and chemotherapy, it still remains dangerous because of the limited efficacy of all the available approaches. Following complete treatment, cancer cells retain the property of metastasis and frequently recur. All the available chemotherapeutic approaches have multiple drawbacks ranging from drug resistance to toxicity (Gupta et al., 2013; Visser et al., 2014). The patient often dies in secondary effect rather than primary disease itself. Thus, there is urgency for developing efficient drugs specific for cancer with no toxicity to normal cells but effective against cancer cells only.

Malaria is a deadly parasitic disease which claims about two million annual deaths worldwide [WHO: World Malaria Report 2012]. It is caused by protozoan parasites of the genus *Plasmodium* (*P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*, *etc.* (Croft, 2010). The spherozoites transmitted by the bite of female Anopheline mosquitoe causes malarial infection in humans (Cox, 2010; Croft, 2010). Even after the discovery and development of several natural and synthetic anti-malarial agents, it is still the leading cause of death as the parasites have developed resistance against most of the drugs currently used to cure this disease (Dondrop et al., 2009). Hence new drugs are required that can overcome this resistance.

Global eradication of malaria demands development of novel drugs with advancement in cost, simplicity and effectiveness against resistant strains (Visser et al., 2014). Drug repositioning is the new approach toward the search for anti-malarial. In this review, we have revisited the repurposing approach of drug discovery and have focused on certain key issues of re-using a molecule that has already been used for the treatment of cancer and has the potential of being used for the eradication or treatment of malaria. Special emphasis has been given on the common mechanism of action of any agent as anti-cancer and anti-malarial.

2. Natural or bioactive compounds

Depending on the broad definition of bioactive/natural products as the compounds derived from living organisms, it is classified as an extract from the organism, an organism itself, a part of the organism and organic compound isolated from an organism. Multiple natural compounds and their derivatives are used for treatment of cancer as well as malaria (Table 1).

2.1. Taxol and its derivatives

Taxol and its derivative paclitaxel are synthesized from the bark of the *Taxus brevifolia* (yew tree) more than five decades ago. Till date it is a well-known naturally occurring alkaloidal terpene based anti-cancer agent which inhibits the tubulin polymerization in cancer cells making the chromosomes unable to achieve metaphase spindle configuration during cell division. This restricts the cells from undergoing mitosis from proper cell cycle regulation and as a result cell undergoes apoptosis (Mekhail and Markman, 2002). But this drug kills normal cells along with cancer cells which cause secondary effects in patients. Recently, some novel derivatives of paclitaxel have been developed to reduce the toxicity and enhance the effectiveness. DHA paclitaxel, a prodrug of paclitaxel, synthesized by conjugating a naturally occurring fatty acid DHA to paclitaxel is currently under phase-II clinical trials. It is effective in a wide variety of cancer such as breast, ovarian, lung and even paclitaxel resistant cancer cells (Bradley et al., 2001). More importantly, a water soluble prodrug, PG-paclitaxel [poly (L-glutamic acid) paclitaxel] have been produced that showed anti-breast and anti-ovarian cancer potentiality. Interestingly, this prodrug displayed a superior anti-cancer action than paclitaxel in terms of enhanced pharmacokinetics and improved therapeutic index (Li et al., 1999). The effectiveness of paclitaxel and its derivatives are not only limited to anti-cancer regime but can also be used to control parasitic infection, like malaria. Interference of taxol/paclitaxel may disrupt the tubular network of the parasite, leading to the formation of deformed parasite which is unable to cause new infection, hence leading to the elimination of parasite from the host (Pouvelle et al., 1994). Recently, Koka et al. (2009) reported that paclitaxel augments eryptosis of infected erythrocytes, thus fostering the clearance of infected erythrocytes from circulating blood. Thus, the compound shows similar mode of action in both cancer and malaria therapy and further exploitation of this compound may prove effective in the development of a single formulation for the treatment of cancer and malaria. A schematic diagram of anti-malarial and anti-cancer action of the drug has been provided in Fig. 1.

2.2. Quinine and its derivatives

Quinine is an alkaloid synthesized from the bark of the chinchona plant. It has multiple synthetic variants such as quinacrine, 9-aminoacridine, *etc.* It is well known for its anti-malarial efficacy and is engaged in malaria treatment since ancient ages. It is effective on the schizoints phase of the parasite and helps in its elimination from the blood stream; it has a gametocytocidal effect

Table 1
Anti-cancer and anti-malarial activity of natural compounds.

Sl. no.	Compounds name	Anticancer			Antimalarial			References
		In vivo	*In vitro*	Mechanism of action	*In vivo*	*In vitro*	Mechanism of action	
1	Betulinic acid	Yes (Mouse model: skin, neuroectodermal, brain)	Yes (head and neck, skin, neuroectodermal, neuroblastoma, brain, blood, kidney)	Trigger the mitochondrial pathway of apoptosis	Yes	Yes	Caspase activation, mitochondrial membrane alterations and DNA fragmentation	Zuco et al. (2002), Thurnher et al. (2003), Ehrhardt et al. (2004), Fulda and Debatin (2005)
2	Quassinoid and its derivatives	Yes (mouse model: colon)	Yes (cervical, colon and pancreatic)	Inhibition of the plasma membrane NADH oxidase	Yes	Yes	Inhibits proteins implicated in DNA synthesis	Morré et al. (1998), Cachet et al. (2009), Huynh et al. (2015)
3	Podophyllotoxin and its derivatives	Yes (mouse model: lung, testicular; clinical trials: liver, lung)	Yes (lung, testicular)	Induces DNA breakage through its inhibition of topoisomerase II	Yes	Yes	Induces DNA breakage through its inhibition of topoisomerase II	Rassmann et al. (1998–1999), Damayanthi and Lown (1998), Kumar et al. (2015)
4	Doxorubicin	Yes (mouse model: breast)	Yes (Colon)	Inhibits topoisomerase activity; upregulates tumor suppressor p53, PTEN and downregulates NFκβ, PI3K, AKT signaling pathway	Yes	Yes	Inhibits the enzyme plasmespsin	Friedman and Caflisch (2009), Bandyopadhyay et al. (2010), Tacar et al. (2013), Li et al. (2015)
5	Dolastatins	Yes (mouse model: lung; phase-I clinical trials: solid tumor, prostate)	Yes (lymphoma, myeloma)	Inhibits microtubule polymerization; arrests G2/M phase of the cell cycle	Yes	Yes	Inhibits microtubule polymerization	Pitot et al. (1999), Kalemkerian et al. (1999), Vaishampayan et al. (2000), Fennell et al. (2003), Sato et al. (2007)
6	Lentinan	Yes (mouse model: oral)	Yes (lymphoma, digestive tract, oral)	Increases IFN-γ producing $CD4^+$ T-cells; reduces IL-4 and IL-6 producing $CD4^+$ cells	Yes	Yes	Activates maturation of DC's; blocks Tregs	Yoshino et al. (2000), Zhou et al. (2009), Harada et al. (2010)
7	Taxol and its derivatives	Yes (mouse model: lung, lymphoma, oesophageal, germ cell, ovarian, breast, head and neck; phase-II clinical trial: ovarian)	Yes (breast, lung, ovary and adeno carcinoma)	Inhibits the tubulin polymerization	Yes	Yes	Disrupt the tubular network of the parasite	Pouvelle et al. (1994), Li et al. (1999), Bradley et al. (2001), Mekhail and Markman (2002), du Bois et al. (2003)
8	Quinine and its derivatives	Yes (mouse model: breast, colon, kidney; phase-III clinical trial: pancreatic)	Yes (breast, colon, lung, glioma)	Induce autophagy; cell cycle arrest; inhibits Wnt-TCF signaling; induces apoptosis	Yes	Yes	Increases the intracellular pH; decreases intracellular transport in parasites; inhibits the transfer of hemoglobin from endocytic vesicle to food vacuole	Schlesinger et al. (1988), Nour et al. (2006), Achan et al. (2011), Mohapatra et al. (2012), Preet et al. (2012a,b)
9	Artemisinin and its derivatives	Yes (mouse model: cervical, breast; phase-I clinical trial: skin)	Yes (glioblastoma, lung, skin, prostate, blood, breast cervical)	Generates ROS; causes oxidative DNA damage and evokes apoptotic pathway	Yes	Yes	Inhibits PfATP6; generates ROS	Singh and Lai (2004), Berger et al. (2005), Morrisseya et al. (2010), Müller and Hyde (2010), Crespo-Ortiz and Wei (2012), Lombard et al. (2013), Luo et al. (2014), Olasehinde et al. (2014)
10	Curcumin and its derivatives	Yes (mouse model: prostate; phase-I clinical trials: colon, pre-malignant lesions)	Yes (breast, colon, brain, prostate)	Suppresses NFκβ pathway; activates caspases, and tumor suppressor genes such as p53	Yes	Yes	Induce ROS production; reduce the production of pro-inflammatory cytokines like TNF, IL12, p40 and IL6	Cheng et al. (2001), Nandakumar et al. (2006), Cui et al. (2007), Mimche et al. (2011), Carroll et al. (2011), Kunwittaya et al. (2014)
11	Resveratrol and its derivatives	Yes (mouse model: skin, breast, gastrointestinal, prostate and lung; phase-I clinical trial: colon)	Yes (ovarian, breast, prostate, skin, lung)	Inhibit cell transformation by acting as an antioxidant, anti-mutagen; induce phase-II drug-metabolizing enzymes; inhibit intracellular protein kinases	Yes	Yes	Inhibits MSP2 fibrillogenesis	Jang et al. (1997), Kim et al. (2003), Mohan et al. (2006), Bishayee and Dhir (2009), Nguyen et al. (2009), Chandrashekaran et al. (2010), Piotrowska et al. (2013), Siddiqui et al. (2013)
12	Vinblastine and its derivatives	Yes (mouse model: lymphoma, bladder, prostate; phase-II clinical trial: solid tumor)	Yes (lymphosarcoma, neuroblastoma)	Disrupts the microtubule assembly	Yes	Yes	Disrupts the microtubule assembly; blocks merozoite invasion	Young et al. (2006), Naughton et al. (2008), Rai et al. (2014)
13	Piperine	Yes (mouse model: breast, sarcoma)	Yes (breast, colon, prostate)	Inhibits p38MAPK, AKT, NFκβ, MMP 9	Yes	Yes	Deregulates UPS	Neto et al. (2013), Do et al. (2013), Ouyang et al. (2013)
14	Camptothecin	Yes (mouse model: renal; phase-I clinical trial: lung)	Yes (breast, lung)	Arrests S phase of cell cycle; inhibits topoisomerase 1 activity	Yes	Yes	Inhibits the topoisomerase 1 activity; blocks the cells in S phase, Wnt signaling cascade	Muggia et al. (1972), Fukuoka et al. (1992), Rothenberg (1997), Bodley et al. (1998), El-Galley et al. (2003), Chu et al. (2014), Hamilton et al. (2014)

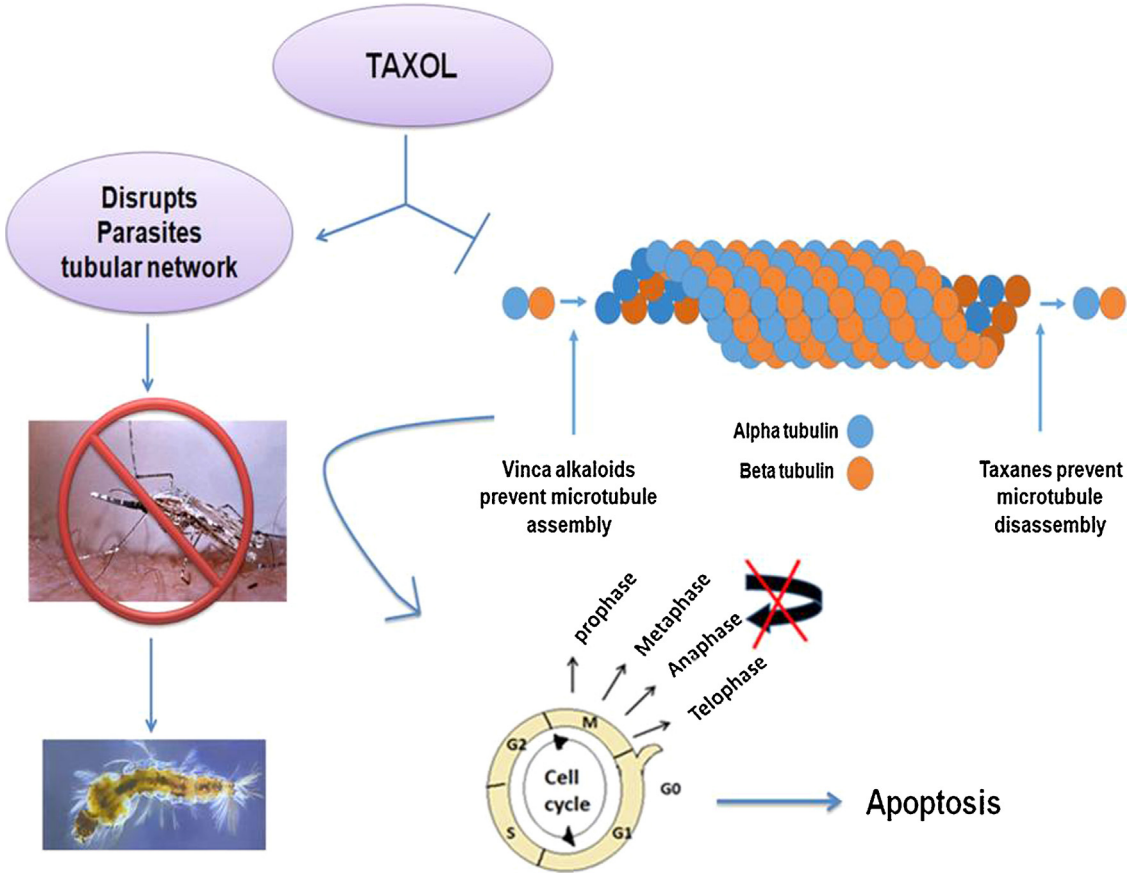

Fig. 1. Representation of mode of action of taxol/paclitaxel in malaria and cancer treatment.

on the *P. vivax* and *P. malariae* (Achan et al., 2011). It increases the intracellular pH by accumulating intracellular cytotoxic heme in food vacuoles and hence decreases the intracellular transport in parasites. It also inhibits the transfer of hemoglobin from endocytic vesicle to food vacuole essential for survival of parasites (Schlesinger et al., 1988). A sub-derivative of quinine, quinacrine (derivatives of 9-aminoacridine) also provides its anti-malarial effect with other derivatives and is effective against multiple number of malarial parasites.

Besides the anti-malarial potentiality, they have also shown effective for the treatment of a wide variety of cancers like lung, gliomas, breast and colon, *etc.* Quinacrine caused breast and colon cancer cell death and arrest in the S phase of cell cycle (Preet et al., 2012a). It also causes cancer cell death *via* autophagy in a p53 and p21 dependent manner (Mohapatra et al., 2012). In combination with lycopene, quinacrine has also shown synergistic effect in killing of breast cancer cells by inhibiting the WNT-TCF signaling pathway. It interrupts the WNT-TCF signaling by increasing the level of APC, DAB2, GSK-3β, AXIN and decreasing the β-CATENIN, p-GSK-3β and CK1 level (Preet et al., 2012b). It also increases the BAX/BcL-XL ratio which in turn, induces apoptosis leading to cancer cell death (Preet et al., 2012a). Combination with TRAIL has also shown increased efficiency of cancer cell death by inducing death receptor mediated signaling cascade (Wang et al., 2011). Thus, one common way of action of quinine and its derivatives in case of both malaria and cancer is through autophagy (Fig. 2).

2.3. Artemisinin and its derivatives

Artemisinin is a natural compound extracted from the leaves of sweet wormwood *Artemesia annua* L. It belongs to a family of sesquiterpene trioxane lactone (Ho et al., 2014) and widely used for anti-cancer as well as anti malarial agents (Posner et al., 2003; Posner et al., 2004). Artemisinin together with its derivatives artemether, artesunate, arteether and dihydroartemisinin are the most widely used drug either singly or in combination therapy for the treatment of malaria in chloroquine resistant *Plasmodium*. Artesunate (ART), a semi synthetic derivative of artemisinin, is significantly more efficient in the treatment of malaria than other derivatives (Luo et al., 2014). When RBC is infected by the malaria parasite, ART consumes the hemoglobin within its digestive vacuole, generating oxidative stress leading to generation of reactive oxygen radicals damaging the parasite and causing its death. It also inhibits PfATP6, the only endoplasmic reticulum calcium dependent ATPase orthologue in *P. falciparum*, which leads to calcium ion homeostasis of the parasite (Müller and Hyde, 2010). Some reports on combination therapy of curcumin and artemisinin have shown its efficacy in removing the drug resistance caused in *P. falciparum* infected malaria (Nandakumar et al., 2006) (Fig. 3).

Besides being used as an anti-malarial drug, artemisinin also extends its efficacy in the treatment of various types of cancer such as glioblastoma, lung and cervical cancer, *etc.* Studies regarding anti-cancer properties of artemisinin show that this drug causes the cancer cell to die *via* generation of ROS, oxidative DNA damage and apoptotic pathway (Singh and Lai, 2004). In cancer treatment, artemisinin acts as radiosensitizers making the cancer cells sensitive to radiation therapy. Artesunate, an artemisinin derivative which radiosensitizes the glioblastoma cells by decreasing survivin and enhancing the nitric oxide (NO) production in lung cancer cells. However, in cervical cancer cell lines, it selectively radiosensitizes the cancer cells *via* abrogation of radiation induced G2/M block and cell apoptosis (Luo et al., 2014). Artesunate also

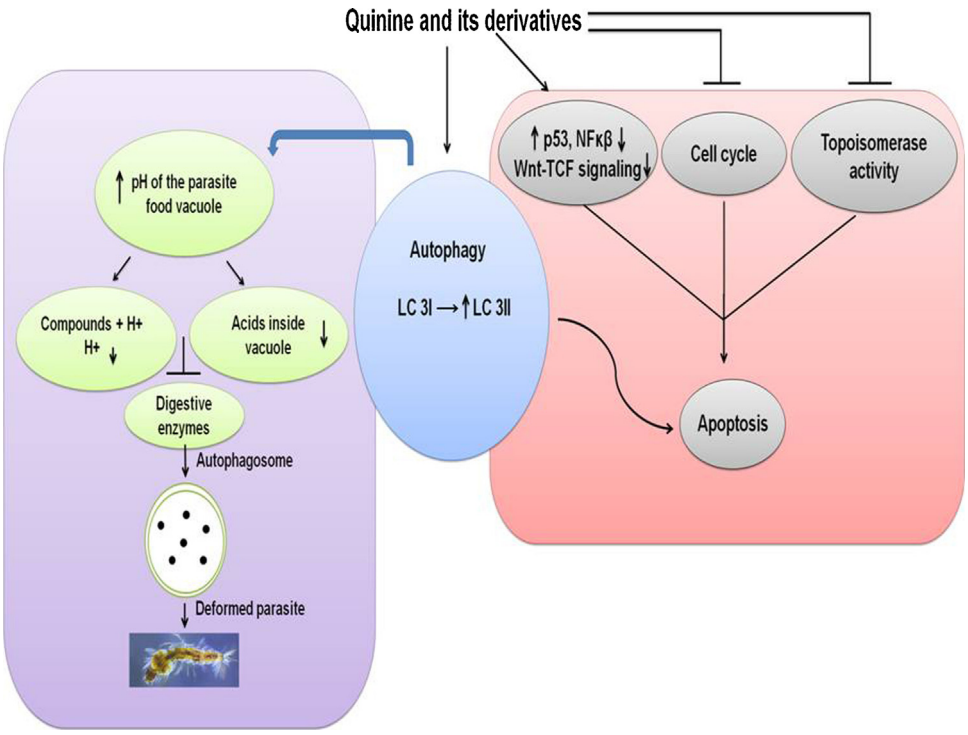

Fig. 2. Schematic representation of various pathways followed by Quinine and its derivatives in treatment of cancer and malaria ↑ and ↓ represents up and down regulation of respective proteins.

inhibits angiogenesis by decreasing the VEGF level. In melanomas, ovarian, prostate, non-small cell lung, leukemia and breast cancer cells artesunate inhibits the cell growth by arresting G0/G1 phase, decreasing CDK2, CDC25A, G2/M arrest and by decreasing cyclin B1 level (Crespo-Ortiz and Wei, 2012). Similarly, dihydroartemisinin another derivative of artemisinin activate caspases, increases the level of Bax, Bak and inhibits angiogenesis by downregulating VEGF, COX2, IL-1β induced p38 MAPK (Morrisseya et al., 2010). The common mechanism of artemisinin and its derivatives attribute toward the efficacy of cancer and malaria therapeutics is through production of free radicals.

2.4. Curcumin and its derivatives

Curcumin is a natural polyphenolic compound isolated from the rhizome of *Curcuma longa* plant. It is commonly known as

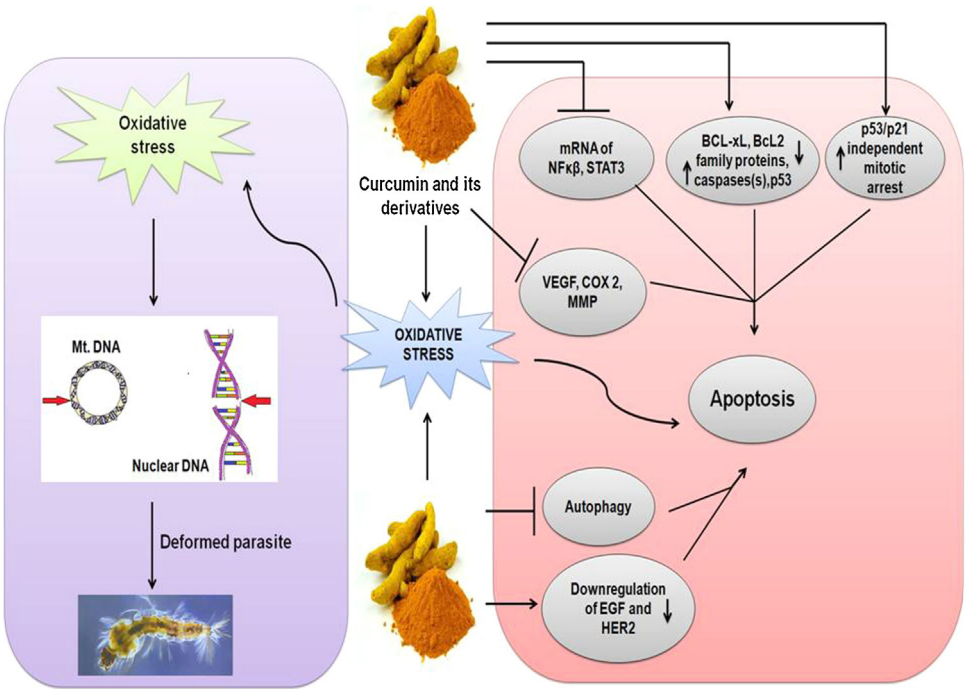

Fig. 3. Schematic diagram representing the mode of action of artemisinin and its derivatives in the treatment of malaria and cancer ↑ and ↓ represents up and down regulation of respective proteins.

turmeric which is used extensively as a spice and coloring agent in food. It has a wide range of pharmacological activities including anti-inflammatory, anti-carcinogenic, and anti-infectious, *etc.* Besides this, it also elicits activities against bacteria, fungi, and protozoa. Recently, available formulation of curcumin consists of about 77% diferuloylmethane, 18% demethoxycurcumin and 5% bisdemethoxycurcumin approximately (Aggarwal et al., 2007). Diacetylcurcumin (DAC), demethoxycurcumin and bisdemethoxycurcumin (bDMC) are the three well known derivatives of curcumin having same mode of action as curcumin. However bis-demethoxy curcumin (bDMC) and deacetyl curcumin (DMC) are more stable than curcumin in physiological medium (Basile et al., 2009). Studies on these curcuminoids have shown that combinations of these derivatives together, are more efficient than administration of a single variant alone (Aggarwal et al., 2007). *In vivo* study of curcumin reported its parasiticidal activity when it is administered synergistically with artemisinin toward *P. berghei*.

In the treatment of malaria, curcumin induces ROS production that leads to cell death through damage of proteins and DNA. Studies on curcumin shows that its treatment leads to mtDNA and nDNA damage and the DNA damage caused was through apoptosis where there was no DNA ladder formation (Cui et al., 2007). Studies involving the treatment of cerebral malaria by administration of curcumin shows that the reduced production of pro-inflammatory cytokines like TNF, IL12, p40 and IL6 in PBMC coupled with trophozoites phase of *P. falciparum* downregulates the expression of ICAM, VCAM1 and E-selectin in endothelial cells where TNF-α activation is found. This down regulation of pro-inflammatory cytokines and adhesion factors after exposure of curcumin *in vitro* leads to activation of NRF2 and PPARγ (peroxisome proliferator activated receptor gamma) that exerts antiinflammatory effects by inhibiting NFκβ transcription factor (Mimche et al., 2011).

The anti-inflammatory property of curcuminoids contributes to its anti-cancer efficacy. It suppresses the activity of transcription factor NFκβ that in turn regulates the expression of pro-inflammatory gene products. In treatment of cancer, curcumin acts in multiple signaling pathways such as MAPK, JAK-STAT3, death receptor, growth factor receptor, *etc.* in multiple cancer such as breast, colon, glioblastoma, prostate, *etc.* A broad discussion on the mechanism of action of curcumin in cancer cell death especially glioblastoma involves down regulation of anti-apoptotic gene products, activation of caspases, and stimulation of tumor suppressor genes such as p53. It also causes cancer cell death by inhibiting angiogenesis, ROS production, autophagy and apoptosis marker, blocking the cell cycle and other multiple pathways.

Curcumin and its derivatives elicit a similar mode of action in both cancer and malaria therapies. Treatment with curcumin leads to production of ROS which in turn leads to generation of oxidative stress. This affects the tumor microenvironment adversely leading to cell death *via* apoptosis and DNA fragmentation. In cancer cells, apoptosis and DNA fragmentation leads to direct cell death and in case of malaria parasite, DNA fragmentation leads to DNA damage and histone hypoacetylation causing death of the parasite (Cui et al., 2007). An overview of different pathways and the common pathway followed by the curcuminoids in the treatment of cancer and malaria is represented in Fig. 4.

2.5. Resveratrol

Resveratrol, chemically known as 3,4,5-trihydroxystilbene, is a natural polyphenolic compound present at least in 72 plant species most of which are consumed by human (Zhang et al., 2014) and enriched in skin of grapes. It has been demonstrated that, trans-Res is an anticancer compound, able to inhibit each phase of cell transformation both in *in vitro* and *in vivo* models, particularly, by acting as an anti-oxidant, anti-mutagen as well as by inducing phase II drug-metabolizing enzymes and also inhibits the initiation, progression phases of tumorigenesis in multiple cellular target including mitochondria, intracellular protein kinases, such as protein kinase B (PKB)/AKT, PKC, MAP kinases, JAK-STAT and transcription factors (*e.g.* p53, pRb, c-JUN and NF-κβ) (Jang et al., 1997; Kim et al., 2003; Mohan et al., 2006). It also arrested the cells in S-G2/M phase and down regulation of cyclins, cyclin dependent kinases and block replication and caused apoptosis.

Though the parent compound Resveratrol, attributes to a plethora of health benefits, its low bioavailability and rapid breakdown to glucuronate and sulphonate finds the way toward new synthetic analogs and derivatives of Resveratrol (Venugopal and Liu, 2012). Pterostilbene (3,5-di-methoxy-40-hydroxystilbene), a dimethyl analog of Resveratrol, inhibits cell proliferation, arrest the cell cycle by down regulating cyclins and CDKs. The substitution of methoxy and hydroxyl group increases the bioavailability of Pterostilbene over Resveratrol. The anti-metastatic property of pterostilbene is due to suppression of MMP, phosphorylation of AKT, p38MAPK and JNK. Petrostilbene also down regulate WNT-TCF pathway components, reduced the expression level of phospho p65 and inflammatory cytokines TNF-α, IL-1β, IL-4 (Fulda, 2010). Another analog of Resveratrol, 3,4,4′,5-tetramethoxystilbene induces apoptosis and cell cycle arrest in G2/M or G0/G1 phase in SKOV-3 ovarian cancer cell by up regulating pro-apoptotic factor BAX, APAF 1 and p53 (Piotrowska et al., 2013). Novel Aza Resveratrol analog inhibited the growth of MDA MB-231, T47D by autophagy, through induction of BECLIN 1 protein (Siddiqui et al., 2013).

In *Plasmodium* species, merozoite surface proteins (MSP) are GPI anchored protein, representing surface coat in these species. They are selective markers for vaccine and drug trials. Resveratrol, along with two flavonoids, EGCG, baicalein inhibits MSP2 fibrillogenesis by disrupting its conformation and leads to parasites death (Chandrashekaran et al., 2010). No extensive study has been carried out in relation to common inhibition pathway of Resveratrol in cancer and malarial parasites.

2.6. Vinblastine

Vinblastine another class of compound (isolated from *Catharanthus roseus*) also exhibits its anti-cancer and anti-plasmodium activity by disrupting the microtubule assembly especially by binding to tubulin polymerase. One of the derivatives of Vinblastine, Vinblastine sulphate has been widely used in the treatment of human neoplasma like lymphosarcoma, neuroblastoma, *etc.* (Rai et al., 2014). It has been reported that it is effective against renal cell carcinoma which normally does not respond to any chemotherapy. The common mechanism of action of vinblastine in malaria and cancer is disruption of microtubule. Hence, it blocks merozoite invasion into RBC and inhibits the cell from progressing through mitosis.

2.7. Piperine

Piperine is a dietary pharmaceutical and a major constituent of *Piper nigrum* and *Piper longum*, generally consumed as black pepper (Srinivasan, 2007). It sensitizes the drug resistant variants of malarial parasites. Plasmodium species contains a gene that encodes Ubiquitin Proteasome System (UPS) regulated by post-translational modification of proteins and it, in turn, regulates the cellular processes. It is reported that certain variant of plasmodium parasites sensitivity increased in combination of piperine and curcumin by deregulation of UPS (Neto et al., 2013).

The anti-cancer effect of piperine has been demonstrated in a wide range of cancer such as prostrate, breast and colon cancer (Ouyang et al., 2013). Several *in vitro* and *in vivo* studies suggested

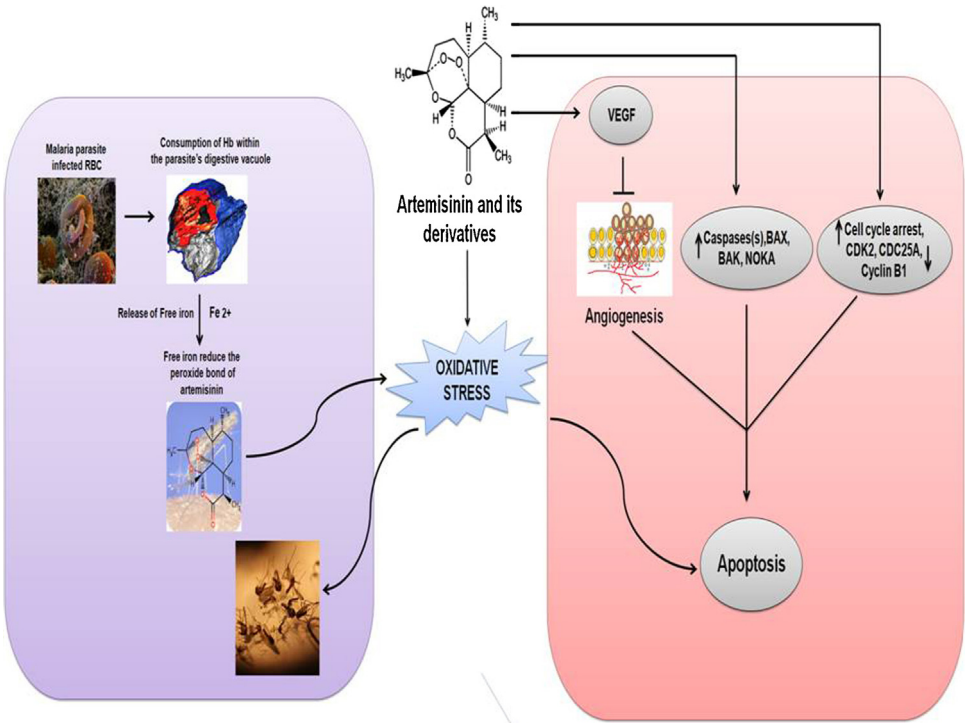

Fig. 4. Figure representing different mode of action of curcumin in cancer and malaria therapy ↑ and ↓ represents up and down regulation of respective proteins.

that it offered its anti-cancer potentiality by inhibiting p38MAPK, AKT, NFκβ and MMP 9 (Do et al., 2013). Co-administration of piperine with docetaxel enhances the anti-tumor efficacy of docetaxel by inhibiting hepatic CYP3α4 which metabolizes docetaxel thereby increasing the half life of docetaxel in plasma membrane (Makhov et al., 2012).

2.8. Camptothecin

Camptothecin (CPT) is a monoterpine alkaloid isolated from *Camptotheca acuminta* (Chu et al., 2014). The primary cellular target of camptothecin is DNA topoisomerase 1. Camptothecin is having its therapeutic potential against a wide range of disease including AIDS, cancer, and malaria (Ramesha et al., 2008).

In *P. falciparum* induced malaria, Camptothecin binds to DNA and RNA and inhibits the topoisomerase 1 activity. It induces cleavable complex formation in the parasite erythrocytic phase and inhibits nucleic acid biosynthesis and kills the parasite (Bodley et al., 1998). Besides topoisomerase activity it also blocks the cells in S phase, WNT signaling cascade, *etc.* The efficacy of its various analogs like CPT-L1, topotecan and 9-AC has been demonstrated against a wide range of cancer cell lines and cancer in Xenograft model (Rothenberg, 1997). The anti-tumor activity of CPT6 and cytotoxicity has been seen in MCF 7 breast cancer cell lines by arresting S phase of cell cycle (Chu et al., 2014). Topotecan has anti-tumor activity in small cell lung cancer. This drug targets topoisomearse I and stabilizes the cleavable complex that leads to fork stalling and DNA double strand breaks in proliferating cells (Hamilton et al., 2014).

2.9. Betulinic acid

Betulinic acid (3β, hydroxy-lup-20(29)-en-28-oic acid) is a naturally occurring pentacyclic triterpenoid (Cichewicz and Kouzi, 2004). Betulinic acid shows a number of biological activities such as anti-retroviral, anti-malarial, anti-tumor and anti-inflammatory. It is generally found in the bark of white birch (*Betula pubescens*) (Tan et al., 2003), ber tree (*Ziziphus mauritiana*), selfheal (*Prunella vulgaris*), flowering quince (*Chaenomeles sinensis*) (Gao et al., 2003), rosemary (Abe et al., 2002) and *Pulsatilla chinensi* (Ji et al., 2002), *etc.*

The mechanism of action of this compound involves CASPASE(s) activation, mitochondrial membrane alterations and DNA fragmentation (Thurnher et al., 2003). There are evidences which shows that this compound and its various derivatives when used at a concentration of IC_{50} value ranging from 175 to 220 nM against *P. falciparum* and chloroquine-sensitive 3D7 strain were found effective and were considered non-toxic (Innocente et al., 2012). Thus, this compound can be used to treat malaria.

Betulinic acid has been found to be effective against various types of cancers (Zuco et al., 2002; Thurnher et al., 2003; Ehrhardt et al., 2004; Fulda, 2008). This compound is effective due to its cytotoxicity and the ability to trigger the mitochondrial pathway of apoptosis in cancer cells (Fulda and Debatin, 2005). There are also reports that this compound in combination with other cytotoxic stimuli suppresses tumor growth, including chemotherapeutic drugs, death receptor ligand TRAIL or ionizing radiation (Fulda et al., 2004). It also triggers CD95 (APO-1/Fas)- and p53-independent apoptosis *via* activation of CASPASES in neuroectodermal tumors (Fulda et al., 1997). There are also reports that normal cells are generally resistant to this compound compared to the cancer cells indicating tumor selectivity (Zuco et al., 2002). This compound has also demonstrated its anti-tumor activity in animal models (Fulda et al., 1999). Hence this compound is potential drug molecule for anti-cancer activities.

2.10. Quassinoid

Quassionoids are a group of natural compounds isolated from *Simaroubaceae* family. There are various types of quassinoids such as Bruceanols, Bruceolide, Eurycomanone, Gutolactone, Isobrucein A, Neoquassin, Nigakihemiacetal A, Quassimarin, Samaderines, Simalikalactones. It shows anti-malarial activity by inhibiting DNA synthesis, and thus protein synthesis (Cachet et al., 2009). It also

causes mitochondrial membrane depolarization and CASPASE 3 activation (Cachet et al., 2009). Quassinoids also show anticancer activity against cervical, colon, pancreas and other cancer cells by different mechanism. In cervical cancer cells it inhibits the cellular growth by reduction of plasma membrane NADH oxidase (Morré et al., 1998). But in colorectal and pancreatic cancer it inhibits the cellular growth by inhibiting p21 activated kinase PAK1*in vitro* and *in vivo* (Huynh et al., 2015).

3. Compound isolated from other living origin

3.1. Doxorubicin

Doxorubicin alternatively known as hydroxydaunorubicin, is a well known anti-cancer drug against colon cancer (Li et al., 2015) synthesized from the red pigment of the microbe *Streptomyces peucetius*. It is an anthracycline derivative having close proximity with the drug daunamycin. Doxorubicin inhibits topoisomerase activity, increases tumor suppressor p53, PTEN and decreases NFκβ, PI3K, and AKT signaling pathway (Tacar et al., 2013). As an anti-malarial, doxorubicin acts by inhibiting the enzyme plasmespsin, an essential peptide of the plasmodia parasites and is unique to the malarial parasite *P. falciparum* (Friedman and Caflisch, 2009).

3.2. Dolastatins

Dolastatins 10 and 15 are naturally occurring small peptides isolated from the marine sea hare *Dolabella auricularia*. Dolastatins acts as tubulin inhibiting agent by binding to the vinca binding region of the tubulin, hence acting as anti-neoplastic agent (meyelomas) (Pitot et al., 1999; Sato et al., 2007). Unlike the role of dolastatin in treatment of cancer, in malaria too, it is assumed that dolastatin inhibits microtubule polymerization hence restricting the parasite to undergo mitosis (Fennell et al., 2003).

3.3. Lentinan

Lentinan, a compound derived from the shiitake mushroom fruiting bodies, possess anti-tumor effects and induces apoptosis in U937 (lymphoma) cell line (Sia and Candlish, 1999). Administration of lentinan to cancer patients leads to the augmentation of IFN-γ producing CD4+ T-cells with the simultaneous reduction of IL-4 and IL-6 producing CD4+ cells, thereby leading to the tilting of Th1/Th2 balance toward Th1 (Yoshino et al., 2000). Lentinan is also used against malarial blood stage infections and involves potent use of Th1 immune responses by activating the maturation of DC's as well as by blocking Tregs, the negative regulators of Th1 (Zhou et al., 2009).

4. Synthetic anticancer drugs

Like bioactive compound various synthetic agents also has potentiality against both cancer as well as malarial parasites (Table 2). A few agents are mentioned below.

4.1. Methotrexate and its derivatives

Methotrexate (MTX) also known as amethopterin, an anti-folate and anti-metabolite drug (Rossi, 2013) is used in treatment of various types of cancer. It is a dihydrofolate reductase (DHFR) inhibitor, an enzyme that plays an important role in the tetrahydrofolate synthesis (Rajagopalan et al., 2002). Methotrexate binds to DHFR with higher affinity than that of its original partner, folate, which is about 1000-fold that of folate (Rajagopalan et al., 2002). Inhibition of DHFR by methotrexate ultimately inhibits the synthesis of DNA, RNA, thymidylates, and proteins (Rajagopalan et al., 2002). This compound acts specifically during the synthesis of DNA and RNA and thus it becomes cytotoxic during the S-phase of the cell cycle. Cancerous cells due to scarcity of dTMP undergo cell death *via* thymineless death.

Studies have been conducted since 40 years to establish the role of MTX as anti-malarial drug. Clinical trials of relatively small scale involving seven patients showed that doses of 2.5 mg per day for 3–5 days were effective in treating malarial infection in humans (*P. falciparum* and/or *P. vivax*) (Sheehy and Dempsey, 1970). It also works in pyrimethamine independent manner of *P. falcifarum* (Kiara, 2009).

Trimetrexate is a MTX analog, which acts efficiently against MTX resistant tumor cells and thereby overcoming the resistance (Wong et al., 1990). It is the most extensively studied folate antagonists which are more lipophilic than MTX and lack the terminal glutamic acid residue necessary for the active transport of the naturally occurring folates and MTX. Like parental MTX it blocks purine biosynthesis thereby inhibiting the synthesis of DNA, RNA and proteins, leading to cell death. It has been widely used against variety of tumors and also been tested in clinical trials for the Leiomyosarcoma of the Uterus (Smith et al., 2002). TMX has shown significant level of cytotoxicity against several murine and solid tumor systems against which MTX is found to be ineffective. Phase II trials in several cancers showed that TMX was well tolerated when it was administered orally at a dose of 5 mg/m^2 twice daily for 5 days, a total dose of 50 mg/m^2/week, given every other week.

It also has good activity against *P. falciparum*, and in combination with the folate derivative 5-methyl tetrahydrofolate (5-Me-THF) does not reduce TMX activity (Nduati, 2008). Thus, TMX in combination with 5-Me-THF could be administrated to increase its safety margin (Nzila et al., 2010). 5-Me-THF is mainly given to protect the host against drug toxicity and it would not negate the anti-malarial activity of TMX. TMX has also been found effective against malaria with a dose of <10–20 mg and the addition of 5-CH3-THF could even improve the therapeutic index of the drug.

4.2. Daunorubicin

Daunorubicin also known as daunomycin cerubidine, initially isolated from *S. peucetius* is a member of the anthracycline family mostly used for the treatment of the various types of cancer (Weiss, 1992). It is mostly used in the treatment of acute myeloid leukemia, neuroblastoma and chronic myelogenous leukemia. It interacts with DNA by intercalation and inhibition of macromolecular biosynthesis which in turn inhibits the progression of the Topo II enzyme that relaxes the DNA during transcription (Pang et al., 2013).

Recently scientists are also utilizing the properties of this compound for the treatment of malaria. Studies confirmed that Daunorubicin with an IC_{50} value ranging from ~3.0 to ~5.0 μM can act as a potential inhibitor molecule for *P. falciparum* UvrD helicase N-terminal UvrD (PfUDN) (Tarique et al., 2014). *P. falciparum* UvrD helicase N-terminal UvrD is essential for the survival of the parasite as its dsRNA showed inhibition of intraerythrocytic development of the parasite *P. falciparum* 3D7 strain. As PfUvrD is absent in human, hence it can be identified as a suitable drug target to control malaria for which compounds like Daunorubicin will be highly essential (Tarique et al., 2014).

4.3. Primaquine

Primaquine (PRI) also known as primaquine phosphate belongs to the 8-aminoquinoline group of drugs that includes tafenoquine and pamaquine. It has been widely studied to increase the sensitivity of resistant cancer cells to anti-mitotic drugs (Tacar et al., 2013).

Table 2
Anti-cancer and anti-malarial activity of synthetic compounds.

Sl. no.	Compounds name	Anticancer			Antimalarial			References
		In vivo	*In vitro*	Mechanism of action	*In vivo*	*In vitro*	Mechanism of action	
1	Methotrexate and its derivatives	Yes (phase-II clinical trial: breast)	Yes (breast)	Inhibits DNA replication and repair	Yes (phase-I clinical trial)	Yes	Inhibits dihydrofolate reductase	Sheehy and Dempsey (1970), Rajagopalan et al. (2002), Nzila et al. (2010), Chilengi et al. (2011), Nicum et al. (2014)
2	Daunorubicin	Yes (mouse model: blood, neuroendocrine)	Yes (blood)	Inhibits Topo-II enzyme	Yes	Yes	Inhibits *P. falciparum* UvrD helicase N-terminal UvrD	Pang et al. (2013), Tarique et al. (2014)
3	Doxycycline	Yes (mouse model: breast)	Yes (colon, breast and prostate)	Inhibits MMP, induces mitochondria-mediated apoptosis in a both caspase-dependent and independent manner	Yes	Yes	Acts against MDR *P. falciparum*	Duivenvoorden et al. (1997), Onoda et al. (2006), Tan et al. (2011)
4	Chloroquine	Yes (mouse model: glioma, breast)	Yes (glioma)	Inhibits Bcl-2 protein family, AKT; increases autophagy	Yes	Yes	Causes drug-DNA complex in parasites which inhibits the parasitic cell division	Emrich et al. (1997), Kim et al. (2010), Cufí et al. (2013)
5	Mefloquine	Yes (mouse model: prostate)	Yes (prostate)	Induce ROS modulated AKT, ERK, JNK and AMPK signaling; autophagy vacuole formation; mitochondrial damage	Yes	Yes	Interacts with phosphotidylinisitol and blocks the membrane transporter system	Harinasuta et al. (1983), Gurova (2009), Klimpt et al. (2011), Sharma et al. (2012), Yan et al. (2013a,b)
6	[(7-Chloroquinolin-4-yl)amino]-chalcone and its derivatives	No	Yes (prostate)	NA	Yes	Yes	Inhibitors of β-hematin formation; inhibit hemozoin formation	Ferrer et al. (2009), Insuasty et al. (2013)
7	Histone deacetylase inhibitor SB939	Yes (mouse model: colon, ovarian, prostate; phase-I clinical trial: solid tumor)	Yes (colon, ovarian, prostate)	Leads to accumulation of acetylated histones and many nonhistone proteins involved in regulation of gene expression, cell proliferation, cell migration, and cell death	Yes	Yes	Causes hyperacetylation of parasite histone and nonhistone proteins	Dokmanovic et al. (2007), Novotny-Diermayr et al. (2010), Razak et al. (2011), Sumanadasa et al. (2012)
8	Pyrimethamine	Yes (SCID mouse xeno-transplantation model)	Yes (metastatic melanoma cell lines	Activates the cathepsin B and the caspase cascade and subsequent mitochondrial depolarization	Yes	Yes	Inhibits dihydrofolate reductase	Gorissen et al. (2000), Giammarioli et al. (2008)
9	Dihydroorotate dehydrogenase (DHODH) inhibitor DSM265	Yes (patient derived tumor xenograft: solid tumor)	Yes	Stall mitosis; blocks cells at S-phase	Yes (mouse model)	Yes	Inhibits dihydroorotate dehydrogenase	Hooft van Huijsduijnen et al. (2013)
10	Tetracyclines	Yes (phase-I clinical trials: refractory solid tumor, kaposi sarcoma)	Yes	Antiangiogenic effect	Yes (phase-II clinical trial)	Yes	Blocks the expression of apicoplast genome	Rudek et al. (2001), Dahl et al. (2006), Richards et al. (2011)

Studies carried out in KBV20C-resistant cancer cells showed that PRI highly sensitized these cells to vinblastine treatment (Edgcomb et al., 1950). Primaquine has been reported to selectively inhibit the formation of functional transport vesicles (Hiebsch et al., 1991). PRI forms a prefusion complex between transport vesicles (donor) and their target membranes but not the destination membrane vesicles (acceptor) (Hiebsch et al., 1991). PRI was reported to inhibit by a donor specific process called priming (Hiebsch et al., 1991).

PRI has also been widely used for the treatment of malaria. It inhibits pyridoxal kinase (Kimura et al., 2014). PRI interacts with the mitochondria of the parasite and prevents it from supplying energy thereby causing death to the parasites, which in turn stops the infection from continuing and thus helping the person to recover. PRI mainly acts on the intrahepatic form of *P. vivax* and *P. ovale* thereby preventing the development of the erythrocytic forms that are responsible for relapses.

4.4. Doxycycline

Doxycycline is an antibiotic of the tetracycline and widely studied for the treatment of colon cancer (Kim et al., 2013). Several evidences show that it can inhibit cell proliferation, invasion and induce apoptosis and block G1 phase in colorectal, breast and prostate cancer cells (Duivenvoorden et al., 1997; Onoda et al., 2006). Doxycycline also reduces the growth of breast cancer tumors in the bone (Duivenvoorden et al., 2002).

Doxycycline is also used for the treatment of malaria. It reversibly binds to the 30S ribosomal subunits as well as the 50S

Table 3
Anti-cancer and anti-malarial activity of nanoparticles.

Sl. no.	Compounds name	Anticancer			Antimalarial			References
		In vivo	*In vitro*	Mechanism of action	*In vivo*	*In vitro*	Mechanism of action	
1	Silver nanoparticles	No	Yes (colon)	Activation of p53 and p21; inhibits NF-κB; induces DNA damage	Yes	Yes	Disrupt the tubular network of the parasite	Ponarulselvam et al. (2012), Satapathy et al. (2013)
2	Gold nanoparticles	Yes (mouse model: lung)	Yes (lung)	Downregulates apoptotic markers; induce anti-angiogenesis activity	Yes	Yes	Up-regulates TGF-β and down-regulates of TNF	Arvizo et al. (2011), Karthik et al. (2013), Kao et al. (2014)
3	Zinc oxide nanoparticles	No	Yes (lung and liver)	Induce activity of caspase-3 enzyme; DNA fragmentation; reactive oxygen species generation, and oxidative stress *via* p53 pathway	Yes	Yes	Inhibits the formation of larvae of malaria vector, *Anopheles subpictus*	Kirthi et al. (2011), Akhtar et al. (2012a)
4	Copper(II) nanohybrid	No	Yes (lung)	Induce reactive oxygen species (ROS) generation; reduce intracellular glutathione (GSH), malondialdehyde (MDA); generates superoxide	Yes	Yes	Inhibits cell growth by affecting *P. falciparum* isolate (MRC-2)	Mohapatra et al. (2010), Valodkar et al. (2012)
5	Nano-curcumin	Yes (mouse model: liver)	Yes (pancreatic and liver)	Inhibits notch signaling pathway; induce IFN gamma secretion and reduce TNFα secretion	Yes	Yes	Inhibits parasite lysate; induce heme polymerization	Bisht et al. (2007), Sasaki et al. (2011), Akhtar et al. (2012b), Yallapu et al. (2013)
6	PLGA based nanoparticles	Yes (mouse model: ovarian, breast)	Yes (ovarian)	Down regulates expression of Bcl-XL and Mcl-1 pro-survival proteins; cleavage of caspase 9 and PARP	Yes	Yes	Distorts the tubular network of the parasite	Yallapu et al. (2010), Surolia et al. (2012)

ribosomal subunit(s) thereby blocking the attachment of aminoacyl tRNA on the mRNA and inhibiting bacterial protein synthesis. It is used in prophylaxis for the treatment against malaria and specifically useful for chloroquine and multidrug-resistant *P. falciparum* malaria (Tan et al., 2011).

4.5. Chloroquinine and melfloquine

A synthetic derivatives of quinine, 4 aminoquinolone *i.e.* chloroquine, showed the similar anti-malarial action with more efficacy than its parental counterpart. It also causes drug-DNA complex in parasites which inhibits the parasitic cell division. Mefloquine, the derivative of Quinine having greater half life with no phototoxicity, is more effective than chloroquine and quinine itself. Intact hemoglobin is essential for the multiplication of parasites inside the host cells. Mefloquine releases the free heme by disrupting hemoglobin in host cells. The accumulating heme moiety is toxic for the parasites and leads to increased ROS production. It also causes death of the parasites by interacting with phosphotidylinisitol which block the membrane transporter system (Klimpt et al., 2011). 9-Aminoacridine, another acridine derivative of quinine is synthesized by crosslinking the heteroaromatic core to different cinnamic acids through an aminobutyl chain. It was effective against the chloroquine resistant strain of *P. falciparum* and also imposes gametocytocidal effect on the rodent parasite, *P. berghei* (Perez et al., 2013).

Mefloquine shows its anticancer activity in prostate cancer cells *via* various ways such as ROS-mediated modulation of AKT, ERK, JNK and AMPK signaling (Yan et al., 2013a,b). Chloroquine causes cancer cell death by inhibiting Bcl-2 protein family, AKT, as well as by increasing autophagy in gliomas. It increases the anti-cancer potentiality in combination with a variety of agents such as anti-folate 5-FU, cisplatin, carboplatin, *etc.* (Kim et al., 2010). A relatively weak base, mefloquine showed its anti-cancer potentiality by autophagic vacuole formation. It increases the well documented marker of autophagy LC3-II production from LC3-I. Besides autophagy, it can induce cancer cell death by degradation of mitochondrial membrane which leads to CASPASE(s) activation and PARP cleavage as well as ROS production. The MDR cancer cells can also be sensitized by mefloquine (Sharma et al., 2012). Being an acridine derivative, they have the property to intercalate with the DNA groove and thus interfere with the cellular processes. They also act by regulating the topo II activities, activation of p53 and inhibition of NFκβ activity, interruption of the cell cycle, protein lipid metabolism, MDM2, *etc.* (Gurova, 2009; Kumar et al., 2013).

5. Nanotechnology

Nanomedicine is the application of nanotechnology to medicine that provides the opportunity to use precisely engineered materials at nanoscale to develop novel therapeutic and diagnostic tools (Table 3) (Liu et al., 2007). Leaf extract of *C. roseus*, *Mimosa pudica* and *Mentha piperita* have gained popularity as ideal bioreductant for the synthesis of silver and gold nanoparticles with high therapeutic potentiality synthesized nanoparticles are against malarial parasites. Starch capped ZnO nanoparticles have shown high efficacy against larvae of malaria vector, *Anopheles subpictus* and filariasis vector, *Culex quinquefasciatus* (Kirthi et al., 2011). Current reports suggest anti-cancer potentiality of Ag, Au, Cu along with other nanoparticles but the detail mechanism of action for both anti-malarial and anti-cancer potentiality need further investigation for a conclusion.

Inspite of the wide usage of curcumin in cancer and malaria therapy, the poor bioavailability, pharmacokinetics, low solubility and high rate of metabolism has limited the use of native curcumin. Recent development in the medical science focus on nano

formulation of this drug that delineates the limitations of free curcumin by increasing the solubility of drug, specificity of drug delivery, extensive stabilization, biocompatibility and improved pharmacokinetics that make it a suitable choice for targeted drug delivery. Polymer, gel and lipid based nanoparticles are among the few alternatives in synthesis of nano formulation of this bioactive compound (Yallapu et al., 2013). Sasaki et al. (2011) developed a nano-curcumin named Theracurmin, which was used in the clinical trial for testing its efficacy on the treatment of malignancy in case of patients suffering from advanced malignancy (ClinicalTrials.gov identifier: NCT01201694). Nano-curcumin acts on the cancer cells in similar mode as that of free curcumin but with slight variations. It acts on cancer cells by inhibition of Notch signaling pathway, increased IFN gamma secretion and decreased TNFα secretion.

Curcumin nanoparticles act on the malaria parasite in the same manner as that of free curcumin. Encapsulation of nanoparticles with lipid base and nano emulsions increases its oral bioavailability, making its administration comparatively easier as compared to the free curcumin and also the duration of disease recurrence after treatment with nano-formulation of curcumin is longer (Memvanga et al., 2013). Curcumin loaded hydrogel nanoparticles synthesized by solvent emulsion-evaporation technique also exhibits anti-malarial efficiency (Dandekar et al., 2010). Ponarulselvam et al. (2012) has recently reported the antimalarial activity of silver nanoparticles synthesized by the *C. roseus* leaf extracts. Similarly, Mohapatra et al. (2010) has revealed the antimalarial activities of the synthesized copper(II) nanohybrid solids against *P. falciparum* isolate (MRC-2). These nanohybrids possess distinct cell growth inhibitory activity.

Polymer coated nanoparticles provide effective therapeutic solutions for malaria. Monensin loaded PLGA nanoparticles have better efficacy toward the antimalarial activity against *P. falciparum* (Surolia et al., 2012). Marine actinobacteria mediated gold nanoparticles possess anti-malarial activity and could be considered in future for anti-malarial drug development (Karthik et al., 2013). Though evidences suggest the effectiveness of anticancer agent against malaria but the common mechanism involved in the mode of action awaits further investigation for any conclusion.

6. Discussion

According to James Black, Noble laureate and a renowned pharmacologist, “The most fruitful basis for the discovery of a new drug is to start with the old drug” clearly describe the repositioning or repurposing approach of developing a known drug for the purpose of targeting another disease (Chong and Sullivan, 2007). Development of novel therapeutic agents against deadly diseases like cancer and malarial infections and expansion of the same into the marketplace is a costly and time consuming process. Drug repurposing/repositioning/reprofiling is the usage of a known drug with already confirmed clinical safety to new diseases. Repurposing approach for the development of drugs considering the drugs already in use, for other clinical diseases is a promising upcoming field of drug discovery.

Cancer, a life threatening disease and a leading cause of global mortality; together with its ever increasing global burden, demand a necessity of drug discovery, although developing novel anticancer drugs remain a challenging task. Similarly, in case of malaria, the global strategy to combat malaria depends upon the diagnosis as well as timely treatment of the disease.

The portfolio of the available anti-cancer and anti-malarial agents somewhere explains a common mechanistic pathway for the treatment of cancer as well as malaria, indicating the usage of anti-cancer as anti-malarial and *vice versa* (Hooft van Huijsduijnen et al., 2013). For instance, naturally occurring bioactive compounds like Taxoland its derivatives (Pouvelle et al., 1994), vinblastine (Rai et al., 2014) and dolastatins act *via* tubular deformation, quinine and its derivative act *via* increasing autophagy (Mohapatra et al., 2012), artemisinin and curcumin generates ROS (Cui et al., 2007), camptothecin and doxorubicin inhibits topoisomerase activity (Friedman and Caflisch, 2009), betulinic acid involves CASPASE activation and DNA fragmentation (Thurnher et al., 2003) and lentinan uses the Th1 immune response both against cancer and malaria respectively. Similar to bioactive compounds, the synthetic counter-parts also has the same potentiality both against cancer and malaria; methotrexate and its derivatives are cytotoxic and act during the S phase of the cell cycle, nutlins leads to G1 and G2/M arrest.

The role of nanotechnology in drug discovery lies in developing new improved drug formulations and effective drug delivery. The small particle size, easy surface permeability, improved solubility, enhanced specificity and increased stabilization of the nano formulated drugs in contrast to their existing counterpart open many boulevards of research in the field of drug discovery for the biologists.

Malaria and cancer are two entirely different diseases with different symptoms; one is a vector borne disease while other is an uncontrolled proliferative disorder. Both the diseases affect a common host and the available drugs share a common mechanism of action for both the diseases. Hence extended combination of these drugs may lead to discovery of a common agent having both antimalarial as well as anti-cancerous properties.

Moreover, developing new formulations and combinations of existing drugs for other diseases is a smart mode of extending the life of a biological entity, the most common requisite of medical science till date.

7. Future direction

The cytotoxic effect of chemically synthesized compounds on the normal cells followed by several side effects paved the way for the extensive research on naturally synthesized compounds to validate its efficiency in treatment of many diseases especially cancer and malaria. The increasing instances of patients gaining resistance to existing malarial therapy has drawn attention to introduce new drug or combination therapy for treatment of this disease. However, development of new drug involves a lot of time and money and moreover the pharmaceutical industry gains a little incentive out of this due to its non-profit market. Hence re-use of existing drugs in treatment of malaria is an attractive strategy that involve low cost and time. In case of anti-cancer drug as the toxicity is already documented at higher doses hence it could be a suitable alternative therapy in the treatment of malaria by some modification, where the mechanism of action is same.

Development in the field of nanotechnology that aims at formulating nanomedicine for treatment of these diseases can also be proved as a potent weapon in the battle against cancer and malaria. Several benefits of these nano-drugs such as their increased solubility, specificity in action, enhanced pharmacokinetics, better stability and bioavailability make these drugs more effective and potent. More explorations in the field of nano-drugs, targeting of a specific protein and a pathway involved in both the diseases can provide better insights in the treatment of the diseases. Using nanotechnology as a single agent having both anti-malarial as well as anti-cancer potentiality will enable us to treat the deadly diseases.

8. Conclusion

Cancer is mainly a non-communicable disease caused by multiple reasons such as genetic, environmental, exposure to

carcinogens as well as other unknown factors. On the other hand, malaria is a communicable disease caused by *Plasmodium* species. One may think that there is no scientific basis for treatment of both the diseases with same drug. However, some time they used similar pathways for diseases manifestation. Thus it can be possible to treat both the diseases by using a drug, having a similar mode of action of treatment for both malaria and cancer (Hooft van Huijsduijnen et al., 2013). The fact that several drugs have a similar mode of treatment may shift the paradigm of drug discovery from one drug-one target-one mechanism to one drug-multiple targets-common mechanism. The earlier approach of searching a specific drug for the treatment of a specific disease as "a specific key for a specific lock" may be shifted to searching a drug with a common mechanism of action for more than one disease as "a master key for multiple locks" keeping in view that the master key should not be able to open all the locks *i.e.* the drug should not have adverse effects (Müller, 2003). In future, nanobiotechnology will be used to combine the drugs which have both anti-cancer as well as anti-malarial activity. Thus same agents can be used to combat two diseases like aiming two sparrows with one arrow.

Conflict of interest

All authors declare that there is no conflict of interest.

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