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USE OF QUINOLINE DERIVATIVES IN CANCER TREATMENT

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Abstract: The quinoline ring plays an important role in many biological systems. Their chemical Synthesis is flexible, can be easily adapted to prepare new derivatives and rationally devised structures, and hopefully can be a source of useful drugs in future. Anticancer activities have been studied for many quinoline derivatives. It has been known that quinoline derivatives may act as anticancer agents through a variety of mechanisms with the most common mechanism being the inhibition of tyrosine kinase isozymes. Several synthesized compounds of quinoline and pyrimidoquinoline having a sulfonamide moiety showed interesting cytotoxic activities. Combination of quinoline nucleues with sulfonamide moieties has received a great attention in seeking for novel anticancer agents. Several quinoline sulfonamide derivatives showed potent anticancer activity as phosphoinisitol kinase (PI3K) inhibitors. Quinoline-benzene sulfonamide nuclei produce potent cytotoxicity against the hepatic cancer cells. Quinolines and pyrimido [4,5-b]quinolines bearing biologically active sulfonamide is a new class of antitumor agents. Potential anticancer agents of a series of tetracyclic indenoquinolines have in vitro antiproliferative activities against breast (MCF-7), lung epithelial (A-549), and cervical (HeLa) adenocarcinoma cells. New quinoline derivatives with high purity and promising cytotoxic effect were synthesized and considered as a good anticancer drug candidate. Some isoquinolines interact either with topoisomerase or they form DNA-intercalated molecular complexes and show promising cytotoxic effect. Recent demonstrations reveal that quinoline carboxylic acid and their analogues can be used as potential anticancer agent. Some isoquinolines interact either with topoisomerase or they form DNA-intercalated molecular complexes and show promising cytotoxic effect. Quinoline derivatives can efficiently inhibit cancer cell proliferation and can be used for treating cancer, especially for treating cancers related to the Janus kinase-signal transducers. Quinoline derivative can trigger transient, p53-independent G2-M arrest in mutant p53 cells (SW620) and succeeding mitotic transition.

Keywords: Anticancer agents, Quinoline derivative, Cancer treatment, Benzopyridine.

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INTRODUCTION

Quinoline is a heterocyclic aromatic organic compound featuring Nitrogen atom as part of the ring system, with the chemical formula C9H7N. It can also be named as, benzopyridine, benzo[b]pyridine, 1- benzazine and benzazine. Quinolines and their derivatives are receiving increasing importance due to their wide range of biological activities such as DNA binding capability [1]antitumor[2,3] and DNA-intercalating carrier[4] and several pharmacologically active synthetic activities.[5-10]

The quinoline ring is one of the most commonly encountered heterocycles in medicinal chemistry and plays an important role in many biological systems [11]. Their chemical synthesis is flexible, can be easily adapted to prepare new derivatives and rationally devised structures, and hopefully can be a source of useful drugs in future.

The utility of quinoline derivatives in the areas of medicine, food, catalyst, dye, materials, refineries and electronics is well established. [12]Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavouring agents. [13]

Quinoline and their derivatives have been extensively explored for their applications in the field of biological[14-16] anti filarial [17]anti-amoebic, antibacterial [19-21] anti malerial, [18,22-27] antifungals[11,18] [28,11,17]antimicrobial [14] anti-leishmanial, [14,11 antimalarial [15]and anti-arteriostenotic and useful in the treatment of , tuberculosis, diabetes, and convulsion , [29,30]

These have been widely used as novel inhibitors. i.e., DHA topoisomerase II inhibitor [31], topoisomerase inhibitor [32], lipoxygenase inhibitor [33],potent HIV-1 inhibitors[18,19] protein tyrosine kinase inhibitor[34,20] These are also extensively used as receptor agonists [35-39]. Cardiovascular and [40]anti neoplastic[41] activities of quinoline derivatives have also been studied.These are also used in protozoal–retroviral co-infections , as anti-HIV-1 agents[42,43] and therapeutic drugs for the inflammatory diseases , for neuro protection in Alzheimer's, Parkinson's, and other neuro degenerative diseases [44].

Various anticancer agents can be designed by topoisomerase inhibition

strategy because topoisomerase play crucial role for the maintenance and replication of DNA during proliferation.Topoisomerase II poisons work by stabilizing the enzyme-induced DNA breaks as anti-cancer agent in clinical use.2,4,6-trisubstituted pyridine containing 5,6-dihydrobenzo[h]quinoline derivatives displayed topo I inhibitory activity and cytotoxicity , if 2-thienyl at 2-position of central pyridine with combination of 2-furyl, 3-furyl, or 3-thienyl at 4-position of central pyridine is present. In terpyridine skeleton

conformationally constrained rigid molecule such as 5,6-dihydrobenzo[h]quinoline moiety may be valuable for the making of antitumor agents.Quinoline aminopurine compound 1 (QAP 1) inhibited topoisomerase II ATPase activity so these drugs may be used in anti-cancer therapy for tumors that bear the appropriate combination of molecular alterations. BRCA1 mutant breast cancer cells displayed increased sensitivity to QAP1 .(+)Camptothecin (CPT),partially decreases tumor initiation when DMBA is applied 16 h after TPA(12-*O*-tetradecanoylphorbol-13- acetate). CPT delays and inhibits promotion of skin tumors the most when applied 12-24 h after each TPA treatment.Because CPT decreases critical DNA replication occuring after the interaction of DMBA with DNA but before the initial DNA damage is repaired so CPT treatment especially reduces the average number and weight of skin tumors/mouse, after DMBA initiate tumours.Some cyanao and amino substituted benzimidazol quinolines,after inhibiting topoisomerase II strong G2/M cell cycle arrest and impairment in mitotic progression. Imidazolyl-substituted compound exhibited pronounced selectivity towards colon carcinoma cells[45].

Inhibition of histone deacetylases (HDACs) is important mechanism in cancer therapy. PIQSA (pyrimido-quinoline benzene sulfonamide)exhibited *in vitro* antitumor activity in a dose dependant manner with strong radio enhancing properties associated with inhibition of HDAC(Inhibition of histone deacetylases) activity, DNA fragmentation followed by apoptotic cell death, preferential cell loss of cells particularly in G1/G0 phase through an apoptotic pathway. PIQSA showed *in vitro* antitumor activity by inhibiting the viability of EAC cell as well as three other human cancer cell lines

(H460), brain (U251) and liver (HepG2). The results of radiation response estimation in Ehrlich solid carcinoma (ESC) tumors suggested that PIQSA exhibited antitumor activities and strong radioenhancing properties related with inhibition of HDAC activity[46-48].

Cryptolepine (5-methyl indolo quinoline), a naturally occurring indoloquinoline alkaloid that interacts with the CC sites of the DNA fragment [49]. In a base-stacking intercalation this is non alternating intercalation and, can be valuable for the design of new anticancer drugs. Indoloquinoline derivatives having 6H-indolo[2,3-b]quinoline , which were substituted at C-2, C-9 or N-6 position by dialkyl(alkylamino)alkyl chains having different number of methylene groups, were cytotoxic against many cancer lines , but displayed high activity against the cells of KB, LoVo, MES-SA and HL-60 cell lines by DNA Topoisomerase II Inhibition.Some of alkyl and alkylaminoderivatives of 6H-indolo[2,3-b]quinolines are known to be active antiproliferative and cell cycle modulating compounds.These derivatives can be compared as the DNA intercalating anticancer drug, ellipticine, and its natural isomer, olivacine.The 5-methylated and respective 6-methylated, 11-substituted 6H-indolo[2,3-b]quinoline derivatives showed anticancer

cytotoxicity and If it was conjugated with 11-(4-methoxyanilino) this new conjugated compound was found most cytotoxic with a mean GI 50 value of 0.78 microM and also exhibited selective cytotoxicities for HL-60 (TB), K-562, MOLT-4, RPMI-8226, and SR with GI 50 values of 0.11, 0.42, 0.09, 0.14, and 0.19 microM respectively. It was observed that 5-methylated derivatives showed higher cytotoxicity than their respective 6-methylated counterparts.Methyl- substituted indolo[2,3-b]quinolines, only derivatives belonging to the 5H series (and none of the 6H series), displayed cytotoxicity against human cervix carcinoma KB cells - ID50 (inhibitory dose 50%) values were in the range of 2 to 9 µM - and against several human cancer cell lines of different origin (ID50 values varied from 0.6 to 1.4 µM), these derivatives showed

topoisomerase mediated DNA clevage [50,51].Indolo[2,3-b]quinoline

Glycosides having daunosamine or acosamine moiety were found cytotoxic

against the cells of human colon cancer (LoVo), uterine sarcoma (MES-SA), promyelocytic leukemia (HL-60), lung cancer (A-549) and melanoma(Hs294T) cell lines.These indoloquinolines showed highest cytotoxic activity against HL-60 and the lowest against the Hs294T and LoVo . Studies conducted on 6H series showed that the introduction of an alkyl-amino-alkyl substituent at the N-6 position of indolo[2,3-b]quinoline accounts for the appearance of the cytotoxic properties against KB cell line.These results indicate a strong relation between 6H-indolo[2,3-b]quinoline derivative's structure and their cytotoxic activity, corresponding well with the ability to bind DNA and to inhibit topoisomerase II activity.Double substituted indolo[2,3-b]quinoline derivatives bearing (dialkylamino)alkyl chains at N-6 and C-2 or C-9 position were tested against various human tumor cell lines and their drug-resistant sublines and the most effective were found, derivatives substituted in position C-2. 5,11-dimethyl-5H-indolo[2,3-b]quinoline (DiMIQ),displayed high cytotoxicity,comparable to the cytotoxic activity of doxorubicin and if conjugated with the guanidinium or a residue of a N-guanylamino acid ,displayed high cytotoxic activity against non-small cell lung cancer A549, breast cancer MCF-7, colon cancer LoVo, cervix carcinoma KB cell lines.

The quinoline imidoselenocarbamate, EI201 blocks the AKT/mTOR pathway and targets cancer stem cells leading to a strong antitumor activity.EI201 treatment reduced, subcutaneous primary tumor 76.5% ,$p < 0.05$ and total tumor burden (76.8% reduction, $p < 0.05$) without showing toxicity in mice. 0.1 µmol/L dose of EI201 triggered a reduction in size and number of tumorspheres in PC-3, HT-29 and MCF-7 cells, and 4 µmol/L dose induced the elimination of almost all the tumorspheres in these studied cell lines[52].

C6, A431, HeLa and MDA-MB-231cell lines revealed the strongest suppressive activity on the proliferation by 8-tosylamino quinoline (8-TQ) ,with IC50 values between 10 to 30 microM. 8-TQ is able to induce

apoptosis and diminished the migration of HeLa cells, and the new generation of blood vessels under non-toxic conditions. Anti-cancer properties were exhibited, by treatment with it, like the specific inhibitors (LY294002 and U0126) of PI3K/PDK1/Akt and ERK [53, 54]. 8-Methoxypyrimid thieno quinoline derivative (MPTQ) is cytotoxic to the cell lines in human promyelocytic leukemia HL-60, melanoma B16F10 and neuro 2a with ID50 range 0.08-1.0 microM. If single and multiple i.p.[intraperitonial] doses of drug used it showed high level activity against the subcutaneous grafted B16melanoma, significantly increasing survival ($P<0.001$) and inhibiting tumour growth .The interaction of MPTQ to DNA occurs by a mechanism of intercalation, which probably accounts for its reported antitumor activity.Single or multiple intraperitonial doses of 4- Oxopyrimido thieno quinoline-(Oxo-PTQ) derivative showed higher level of activity against the subcutaneous grafted B16F10 melanoma with a significant increase in life span.This research offered a new intercalation functional group to DNA targeted drug design.7-oxo-7H-naphtho[1,2,3-de]quinoline derivatives having one or two basic side chains and containing different substitution on pyridone ring exhibited cytotoxic activity against sensitive human leukemia cell line HL-60 and its resistant sublines HL-60/VINC and HL-60/DX. [55]

Pyridine and quinoline sulfides bearing dimethylheptylsilyl group at the sulfur atom had cytotoxic effect (> 15.5 g/mL). If The dimethyl heptylsilyl group was substituted by trimethylsilyl or silahexyl group, cytotoxicity was increased.8-trimethyl silyl methyl mercaptoquinoline exhibited the highest activity among quinoline sulfides and exhibited toxicity on HT 1080 cells(2.5tg/mL) and MG 22A with 3.5tg/mL.

Some compounds having a quinoline scaffold and a flexible, semi-flexible or rigid side chains at position 8 of the quinoline ring ,showed more refractory cytotoxic activity to the HT29 cell line,most compounds were found to exhibit moderate activity against MDA-MB231 with IC50 values ranging between 4.6 and 48.2 µM, and Schiff's base derivative of this was the most active with IC50 of 4.7 and 4.6 µM against HT29 and MDA-MB231, respectively[56] .

Chloro-quinoline amino derivative “CITme appears to act as a

topoisomerase II inhibitor,and potentially selective for cervix adenocarcinoma and/or prostate cancer .If cancer cells (DU-145, HeLa, CoLo, MCF-7 and Jurkat cells) were treated with CITme ,DU-145 cells appeared to be the most sensitive ,for three days and CITme was more cytotoxic against HeLa cells, with IC50 of 0.872 µM, followed by DU-

145 with an IC50 of 2.543 µM,after seven days treatment.7-chloroquinoline derivatives bearing the biologically active benzenesulfonamide moiety exhibited anticancer activity . 4,7-dichloroquinoline compound was the most active compound of this series, with IC(50) value 64.41, 75.05 and 30.71 µM compared with Doxorubicin , with IC(50) values 82.53, 88.32 and 73.72 µM on breast cancer cells, skin cancer cells and neuroblastoma, respectively[57,58].

4-(4- Acetylphenylamino)-6-methoxy-2-phenylquinoline derivatives(ketone precursor), were found especially active against the growth of certain solid cancer cells such as NCI-H226 (non-small cell lung cancer), MDA-MB-231/ATCC (breast cancer), and SF-295 (CNS cancer) with GI50 values of 0.94, 0.04, and < 0.01 µM respectively.Its oxime , and methyloxime , also exhibited significant cytotoxicity against all 60 cancer cells with mean GI50 values of 3.89, 3.02, and 3.89 µM, respectively. Substitution of the carboxylic acid at C(3) prevent it's phenyl ring to lie coplanar with quinoline, which is the reason of lack of cytotoxicity in it.So 4-substituted-4-anilino-derivatives are more cytotoxic than their respective 3-substituted-4-anilino- counterparts.4-amino-3-acetylquinoline derivative showed cytotoxic activity on tumor cell line L1210, the IC100 values were 50 µg/ml (for 24 h), 25 µg/ml (for 48 h) and 10 µg/ml (for 72 h). The IC50 value was found to be less than 4 µg/ml , as a potential anticancer drug according to the National Cancer Institute (NCI).

Indeno[1,2-c] quinoline derivatives have the potential of dual top I and top II inhibition. For these compounds,substitution of C11 is important for anti proliferative activities in which the terminal amine preferred to be a tertiary or the cyclic five membered pyrrolidino ring .Some oximes of these revealed high cytotoxicity with GI50 value of 0.84,0.89 and 0.79 micro M against , SAS ,A549 and BT 483, respectively which is more active than campothecin, Substitution at C6exhibited selective cytotoxicity.These derivatives displayed a positive correlation among anti proliferative activity,DNA binding affinity and dual topo inhibitory activities [59]. Tetracyclic indenoquinolines formed between purpurogallin derivatives and nitrosobenzene displayed *in vitro* antiproliferative activities in the µM to nM range against breast (MCF-7), lung epithelial (A-549), and cervical (HeLa) adenocarcinoma cells .These compounds exhibited correlation between the activity and their aromaticity and planarity as topoisomerase poisons,which was similar to or better than that of camptothecin.Some triazolyl-indenoisoquinoline derivatives showed significant activity against human lung (HOP62), ovarian (OVKAR3), breast (ZR751), leukemia (HL60) and prostate (DU145) cancer cell lines,compared with the doxorubicin as a reference drug.[60] Compounds containing quinoline moiety with thiosemicarbaides exhibited interesting anticancer activities against HCT116 cancer

cells.There are two possible ways of exhibition of anticancer potency through blocking of Ribonucleotide reductase (RR)[61-64] or by specific redox activity[65] .

Tetracyclic quinoline and quinoxalinecarboxamides showed cytotoxicities broadly similar to those of the mixed topo I/topo II inhibitor DACA, and displayed up to 3 fold more cytotoxicity than DACA in the human leukaemia cell lines and in colon comparable to that of doxorubicin.

Novel pyrrolo-quinoline derivatives bearing the methanesulfon-anisidide side chain or lacking the methoxy substituent, exhibited interesting cell growth inhibitory properties specially in those obtained from solid tumors like CNS-, melanoma- and prostate-derived cells. Most active proved to be compound which lacks both methyl and methoxy substituents, followed by compound having the methoxy group only[66].

A novel imidazo[1,2-a]quinoxaline derivative compound , EAPB0203 exhibited *in vitro* cytotoxic activity on A375 and M4Be human melanoma cell lines .

Various pyrazolo[3,4-b]quinoline ribofuranosides were evaluated by Ronald Wolin *et al*. [67] and compounds were found to be most active in *in vitro* studies for their ability to inhibit the nucleotide exchange process on oncogenic Ras gene .If a positive charge density at carbon-7, a side chain at position C-2 or C-9 of the thiazoquinoline skeleton with two basic nitrogens and pKa value of 7.5 -10 in the most basic center, and a conformational flexibility of this basic side chain are present in 9 hydroxy and (alkyl amino) thiazolo[5,4-b]quinolines they exhibited anticancer acivity.9-anilinothiazolo[5,4-b] quinoline derivatives showed DNA binding in nanomolar(nM)range[68] and compounds having N,N-diethylamino)ethyl]amino group showed the best cytotoxic activity in several cell lines[69].3 substituted quinazoline derivatives used as an excellent anti tumor agent due to their EGFR-tyrosine kinase inhibitory activity .EGFR PTK have great therapeutic potential in the treatment of malignant and nonmalignant epithelial diseases.Nitro imidazolypropylamino derivative (NLCQ-1) show significant hypoxic selectivity in several rodent and human tumor cell lines because of its weak DNA-binding [70].After 4.5 h exposure,selectivity can be increased up to 388-fold.NLCQ-1 substantially enhances, in a schedule-dependent manner, the antitumor effect of alkylating agents, as well as 5-fluorouracil and paclitaxel against murine tumors and human xenografts cyclic amidino-substituted derivative of benzimidazo[1,2-a] quinoline , displayed anti proliferative effects on SW620 cells and mitotic cell death seemed to be the primary mode of death in these cells.[71] In colorectal carcinoma (HCT 116),it induced p53-dependent apoptosis. This compound played as catalytic inhibitor of topoisomerase II and also have intercalative property via its benzimidazo[1,2-a]quinoline moiety.Benzimidazole-4,7-diones compounds

containing the thiomethyl group or the 2-pyridyl moiety, at the 2-position ,displayed high activity on human non-Hodgkin lymphoma.

2-Aryl-3-bromoquinolin-4(1H)-ones (QNHFBr and QNHClBr), and the 3-bromo-2-(4-chlorophenyl)-1-methylquinolin-4(1H)-one (QNMeClBr) showed antiproliferative activity and increased cytotoxicity at higher doses.[72] Low levels of proangiogenic factors, namely, basic fibroblast growth (bFGF) and vascular endothelial growth factor/placental growth factor

(VEGF/PlGF) were obtained in culture in which these compounds were

treated because QNHFBr and QNHClBr compounds inhibited neovessel growth so these compounds can work as antiangiogenic agent.The cytotoxicity of 2,5- diaryl series compounds were attributed in-part to their weak to medium antimitotic activity [73] .Its methoxy derivatives displayed the highest cytotoxic activity in structure–activity relationship study.2,3-Diarylquinoline derivatives explored potent anticancer activity against six cancer cell lines, including human hepatocelluar carcinoma, non-small cell lung cancer and breast cancer, compound that was more active than tamoxifen,induced cell cycle arrest at the G2/M phase .

Quinoline derivatives, MS-073, exhibited similarity to verapamil to overcome MDR(multidrug resistance) *in vitro* and *in vivo*. At low doses MS-073 exhibited higher MDR .I.P.(intraperitoneal) daily dose for 5 days enhanced the chemotherapeutic effect of VCR(vincristine) in VCR-resistant mice ,if it was given with VCR. [74]

6 h (9-(3-Bromo-phenyl)-4-phenyl hexahydro-4H-cyclopenta [b] quinoline-1, 8-dione having bromophenyl moiety, if substituted phenyl on nitrogen of central quinoline ring of this structure ,exhibited cytotoxic activity especially in Raji and HeLa cell ines , with IC30: 82 and 24.4 microM respectively .Although anti cancer effect of these compounds is low but this structure can play benificial role to develop and design novel potent compounds by its cytotoxic activity.[75]

5,7-Dibromo-1,2,3,4-tetrahydro-2-methylquinolin-8-ol showed similar cytotoxic effects on Hep3B, HKESC-4 and A549. This compound - (10 mg/kg/day) is effective in suppressing the volume growth of the KYSE150 xenograft tumors.

1:1 Schiff base copper complexes of quinoline-2 carboxaldehyde displayed dose dependent,anti proliferative,and proapoptotic activity in PC -3 and LNCaP prostate cancer cells IC50of 4 and 3.2 micro M,respectively [76]

MeDZQ, a quinone induced apoptosis in human colon adenocarcinoma cell lines , HT29 and BEcells, but more effectivly on HT29 cells.[77] Pyrimido[4,5-c]quinolin-1(2H)-one derivatives displayed anticancer activity

by the antimigratory and cytotoxicity and methoxy groups are very important for these activities. Antimigratory activity can be improved if the 2-methoxy and 2,4-dimethoxy groups are substituted at the 2-aryl- pyrimido in the 9-methoxy-substituted series and the 3,4,5- trimethoxy moiety is substituted at the 2-arylpyrimido group , in the presence or absence of the 9-methoxy substitution.Antimigratory property of these compounds is useful to control metastatic breast cancer. [78]Certain derivatives of pyrimido[4,5-b]quinoline and [1,2,4]triazolo[20 ,30 :3,4]pyrimido[6,5-b]quinoline skeletons whose rigidity might contribute to a potential DNA-binding affinity and antitumor activity has been studied [79] .Qunolines, hydroquinolines and hexahydropyrimido[4,5-b]quinolines are important building blocks of different efficient anticancer compounds Some of its derivatives , containing sulfonamide moiety fulfilled the requirements of inhibition of carbonic anhydrase (CA) isozymes so they displayed anticancer activity. Compounds showed IC(50) 71.8 microM against human breast cancer cell line (MCF7),comparable to reference drug doxorubicin.Most of the compounds of pyrimido[4,5-b]quinolines and triazolo pyrimido[6,5-b]quinolines showed moderate activity against MDA-MB-231, and HT-1080 cell lines. , HT-1080 was more susceptible than MDA-MB-231 cell lines. The C-9 methoxy group was found to reduce the cytotoxicity compared to other compounds lacking this group in the same position.Some quinolines and pyrimido[4,5-b]quinolines displayed higher activity with IC50 values (5.5, 6.9, 7 μg/ml) when compared with Doxorubicin as a reference drug (IC50 value 38 μg/ml).N-amidino-substituted benzimidazo[1,2-α]quinoline derivative induced a p53-dependent response in HCT 116 resulting in accumulation of the G1- and S-phase cells and induction of apoptosis via both caspase-3-dependent and caspase-independent pathways.This compound exhibited antiproliferative effect on SW620 cells. So it can be used as an antimetastatic agent[80].The low-molecular-weight imidazoquinolinamine derivative, oral dose in transplantable murine tumors. Oral treatment with 30 mg/kg imiquimod once every three days significantly inhibited MC-26 colon carcinoma.Delay of treatment from day 1 to day 5, when tumors were easily palpable, did not reduce benefits. Ten daily treatments were slightly more effective than five. Tumor growth level was same if the total dose delivery of imiquimod was same , either once every day for 20 days, once every 4 days, once every 7 days, or once every 10 days ,it is the effect of (IFN-α) induction .If imiquimod treatment was given with cyclophosphamide ,effect was significantly($p < 0.01$) better than used either drug alone. Imiquimod also inhibited the growth of RIF-1 sarcoma and Lewis lung carcinoma.[81]

The small size of imiquimod, its hydrophobicity and ability to penetrate the epidermal barrier are good for systemic application but it shows unwanted side effects so topical formulation (Aldara 5% cream) was developmed for the treatment of viral lesions (HPV papillomas) and malignant tumors of the skin.Imiquimod is also effective against a variety of primary skin cancers as well as cutaneous metastases of some malignancies. Cutaneous tumors that have responded well to topical treatment with imiquimod include basal cell carcinomas [82-86] keratoacanthomas[87] actinic keratoses [88-92] and Bowen's disease (the latter two entities represent epidermal carcinoma *in situ*[93,94] cutaneous metastases of melanoma [95-99] some cases of primary melanoma *in situ* [100-104]and cutaneous T-cell lymphomas [105-108]. Imiquimod have also been observed in difficult-to-treat patient populations, such as organ transplant patients under immunosuppressive therapy [109] or Xeroderma pigmentosum patients suffering from rapid development of multiple UV-induced cutaneous malignancies [110] ,by topical application.

A quinine-3-carboxamide,Linomide was effective in treatment of prostate cancer due to its anti-angiogenic effects .Antitumor effects of linomide against rat prostatic cancers may involve both immune and nonimmune host mechanism(s) (e.g., antiangiogenesis).Due to Cytotoxicity, growth rate was retardated(i.e., increased tumor volume doubling time) of primary prostatic cancers and in metastatic lesions .It's growth retardation is reversible, so continuous daily treatment with linomide is required to get maximal antitumor response.Isomeric phenylquinoline-8-carboxamides that intercalate show *in vivo* antitumor activity, with the 2-phenyl derivative in particular possessing broad-spectrum activity [111].

Tasquinimod is the lead second-generation orally active quinoline-3-carboxamide, Tasquinimod show antiangiogenic activity and do not show pro-inflammatory effects because it contains substitution in the 5-position of the quinoline moiety and a substitution in the phenyl ring of the 3-carboxamide moiety. It has both antitumor and anti-metastatic activities, which are affected mainly through its anti-angiogenic and immunomodulatory effects . In a preclinical study by Jennbacken *et al*[112], it was observed that tasquinimod mainly inhibit the initial establishment of metastatic deposits and had lesser effect on inhibition of growth of already metastasized deposits [113].Tasquinimod acts through multi-targeted mechanisms to treat prostate cancer .Tasquinimod had been reported to bind to histone deacetylase (HDAC)-4.The HDAC-4/NCOR/HDAC-3 complex is needed for deacetylation of HIF-1α (transcription factor) and of histone proteins around the DNA . The prevention of deacetylation of HIF-1α by tasquinimod leads to inhibition of VEGF transcription[114]. Tasquinimod also reduced the number of peripheral and tumor-infiltrating granulocytes.When tasquinimod was

combined with androgen ablation or radiation therapy antitumor activity was improved in prostate cancer , combination of tasquinimod with peptide vaccine SurVaxM has been reported to reduce tumor growth. Combination of tasquinimod either with sipuleucel-T or with docetaxel displayed superior anticancer efficacy and improved survival for the Castrate-resistant prostate cancer (CRPC) patients.

In a study,PQ1 reported to decrease the viability of cancer cells and attenuate xenograft tumor growth. There was increment in cleaved caspase-3 in PQ1-treated cells. It can be said that PQ1 induces cytotoxicity via activation of both caspase-8 and caspase-9 because PQ1 can activate the intrinsic checkpoint protein caspase-9, enhance the level of pro-apoptotic protein Bax, and release cytochrome c from mitochondria to cytosol. Approximately 80-95% growth attenuation was exhibited by PQ1 in multiple breast and colorectal cancer cell lines and it showed 20-50% increase in junctional intercellular communication(GJIC) in these cells. Second generation substituted quinoline compound(PQ7), was more powerful enhancer of GJIC activity in cancer cells, than the first generation substituted quinolines PQ1[115,116]. PQ7 was utilized as a treatment for mammary carcinoma in a spontaneous mammary tumor mouse model .Tumor growth was attenuated by PQ7 with a final tumor volume of 27.8 mm3 over the 14-day treatment period but final volume of control DMSO (di methyl sulfoxied) treated mice was 377 mm3. PQ7 significantly reduces tumor volumes during the Pre stage of development but for enhance killing of the neoplastic cells in late stage it should be used in combination with other chemotherapeutic options. Because PQ7 treatment increased Cx43 expression in the neoplastic tissue, only during pre-tumor formation but not in late stage .Tumor bearing animals showed 98% reduction in tumor growth,with the PQ7 treatment.Activation of apoptotic signaling is an important mechanism of anti-cancer drugss which induces cytotoxicity.

Luzopeptins are a family of new antitumor antibiotics [117-124]that contains 2 substituted quinoline chromophores linked with a cyclic decadepsipeptide in a 2-fold symmetrical manner . In the luzopeptin A molecule, the hydroxyl groups of both tetrahydro-pyridazine moieties of the peptide ring are acetylated, whereas only one of the 2 tetrahydropyridazines ,is acetylated in luzopeptin B, and none is acetylated in luzopeptin C.Studies of antitumor activities[122,123] in the experimental tumor model luzopeptin A was very active, it was 100- to 300-fold higher than that of mitomycin, luzopeptin B was approximately 3-fold less active than luzopeptin A, whereas luzopeptin C was virtually inactive . This remarkable difference in antitumor activity was from the different degree of acetylation of the non-chromophore peptide ring portion [125].

After intraperitoneal injection of MH134 tumour cells,vesnarinone (dimethoxybenzoyl piperazin quinoline derivative) -at concentration of 30 mg/kg body weight increased the mice survival rate from 15.7, in the untreated control group to up to 21 days [126].

Rapid chemical inhibition of lactate dehydrogenase(LDHA) by3-((3-carbamoyl-amino) benzoic acid derivatives of quinoline, were identified as NADPH competitor. This quinoline 3-sulfonamids altered and impaired cell

survival in carcinoma cells to treat solid tumors for which aerobic glycolysis is necessary to survive and promoted apoptosis in Snu398 cells.[127]

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