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Kulvinder Kochar *

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Review Article

Greater Efficacy of Treating Drug Eesistant Breast Cancer with Combined Endogenous Hydrogen Sulfide Generating Enzymes Targeting [Cystathionine-β – synthase, Cystathionine -γ-lyase&3 Mercapto Pyruvate Sulfur Transferase-over Single Enzyme targeting -- A Short Communication

Kulvinder Kochar Kaur [1]*, Gautam Nand Allahbadia [2], Mandeep Singh [3]

[1] M.D (Obst & Gynae, specialist reproductive endocrinology & Infertility specialist). Scientific Director cum Owner Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India,

[2] M.D. (Obst & Gynae), D.N.B Scientific Director Ex-Rotunda-A Centre for Human Reproduction Mumbai, India

[3] M.D.DM.(Std)(Neurology) Consultant Neurologist, Swami Satyanand Hospital Punjab.

***Corresponding Author:** Kulvinder Kochar, M.D (Obst & Gynae, specialist reproductive endocrinology & Infertility specialist). Scientific Director cum Owner Dr Kulvinder Kaur Centre for Human Reproduction, Punjab, India.

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Abstract

Leukemia stem cells (LSCs) possess several key properties of normal cells including self -renewal, unlimited proliferative potential, infrequent or slow replication. Leukemia initiating cells (LICs) refer to all cells with leukemia- initiating potential and/or LSC capacity. Actually, our definition for leukemia initiating cells requires that those cells should be capable of self-renewal which resulting in the appearance of progeny that share the ability of self-renew as well.

Keywords: leukemia initiating cell; leukemia stem cell; malignant hematopoietic microenvironment

Introduction:

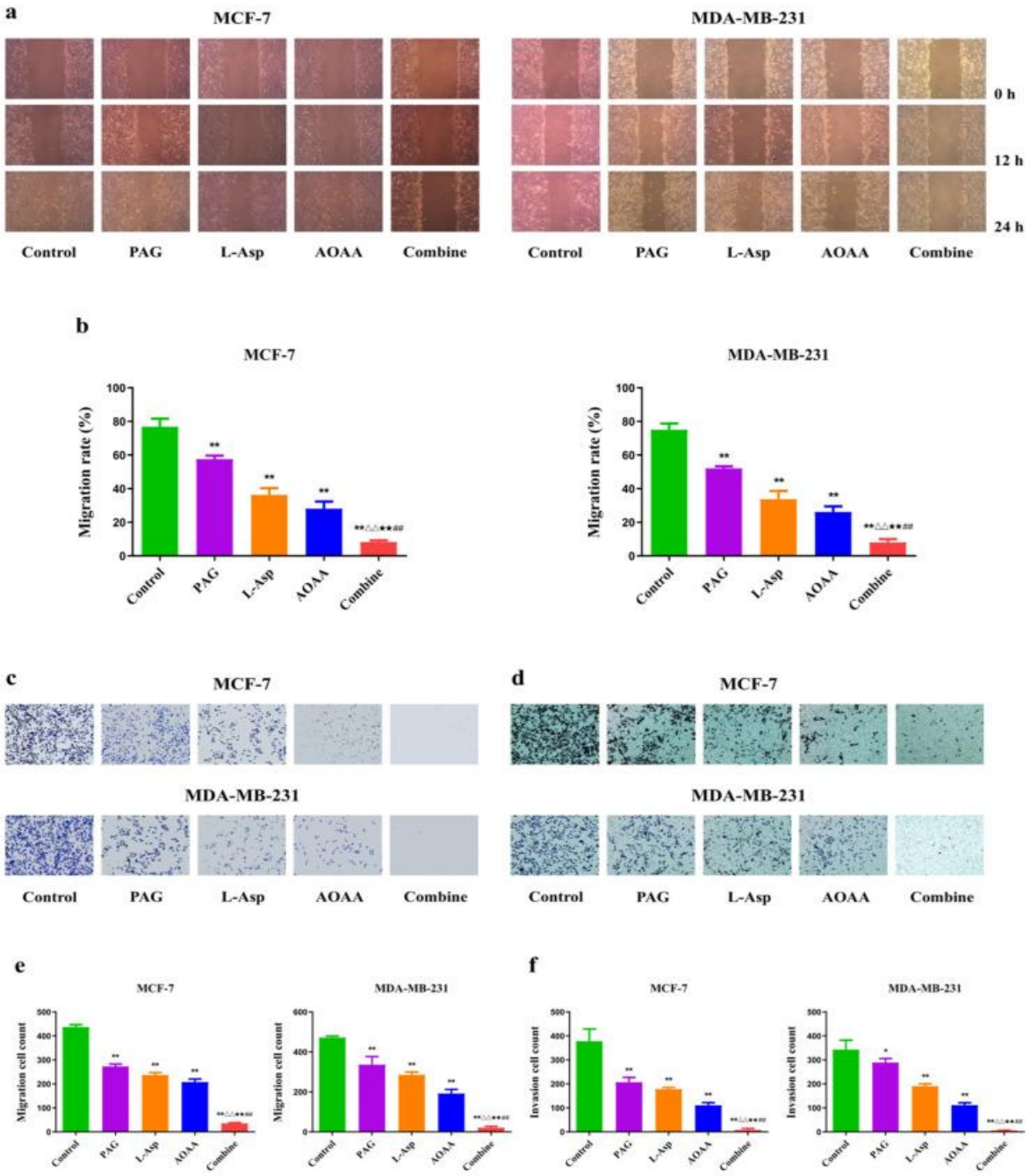
Breast cancer(BC) represents a malignant tumor which takes place In the mammary epithelium whose prevalence has considerably escalated in women throughout the world [1].As per recently, revealed about2.3 million cases are having a diagnosis of BC/year with a yearly mortality of approximately 450,000 [2].Major correlated risk factors of BC are inclusive of age, the prevalence of genetic mutations in susceptibility genes (BRCA1 as well as BRCA2),lifestyle dependent modifications (non genetic) risk factors, nulliparity, early menarche, initial pregnancy subsequent to 30yrs of age, elderly age of menopause, utilization of Oral contraceptives (OC) in addition to family history of BC along with other clinical complaints [3]. Hydrogen Sulfide (H2S), along with nitric oxide (NO), carbon monoxide (CO) are implicated in modulation of numerous physiological as well as pathological events. H2S has been broadly considered to be an endogenously produced gasotransmitter molecule [4]. in case of normal physiological circumstances 3 enzymes broadly expressed in mammalian tissues along with cells for instance Cystathionine-beta - synthase (CBS), Cystathionine -gamma-lyase (CSE), in addition to 3 mercaptopyruvate sulfurtransferase (3-MPST)-generate H2S [5]. H2S illustrates pleiotropic as well as usually dose based actions subsequent to its liberation as acid labile sulfur along with bound sulfane sulfur [6]. It has been well acknowledged that H2S is implicated in the modulation of necessary cellular modes, possessing the key part in the controlling of the numerous physiological situations, inclusive of energy generation, neuroprotection, vasorelaxation, glucose homeostasis along with angiogenesis [7]. Specifically, the part of H2S in cancer, it has been revealed that endogenous H2S is responsible for cancer generation in addition to propagation [8]. With regard to cytoprotective biological reactions, H2S is believed tobe a bidirectional therapeutic target with regard to cancer research. While certain studies illustrated that exogenous exposure to H2S donors avoids tumor generation [9]. Conversely other studies have illustrated that reduction of H2S quantities by

downregulation of the generation of the endogenous H2S existent in the cancer cells result in diminished cancer propagation [10]. With these robust therapeutic properties with regard to cancer research, H2S has gained considerable interest of numerous scientists in addition to drugs possessing the capacity of repression of or initiation of the generation or facilitate the liberation of H2S has achieved remarkable interest in preclinical along with the clinical scenarios.

With regard to promoting **f**urther clinical translation of this scientific work in addition to the posit of attractive strategies regarding therapeutic modulation of the H2S, variable innovative hampering agents have been generated for repressing the actions of the H2S generating enzymes. Presently 3 substances whose properties have been pharmacologically well evaluated for instance DR proparglycine (PAG), L-aspartic acid(L-Asp) along with aminooxyacetic acid (AOAA)-are believed to be competitive robust hampering agents of CSE, 3-MPST, CBS respectively were chosen. PAG($C_5H_7NO_2$) portrays a selective hampering agent that primarily results in blockade of the active region of the CSE enzyme, thus avoidance of its binding to the original substrate. This agents solubility is significantly greater in both water along with PBS[11].L-aspartic acid(L-Asp) ($C_4H_{14}NO_4$) acts in an akin fashion to PAG .This agents solubility is germanely lesser- about 50% of that of PAG in water[12]. Akin to numerous studies AOAA has further been revealed to decrease H2S generation by hampering the working of CBS in the acidic in addition to prodrug kinds. AOAA has been displayed to decrease intracellular adenosine triphosphate (ATP) quantities in addition to diminished glycolysis rate by which it has the capacity of controlling cellular actions. Numerous studies have illustrated the selectivity of AOAA; nevertheless, it further hampers CSE. The action of the AOAA is quantity based in both water along with PBS [11,13]. With the acknowledgement of promising outcomes hampering H2S generation, it is of significance in evaluating the electrostatics (protonation as well as deprotonation status) of such agents in solution in addition to physiological situations.

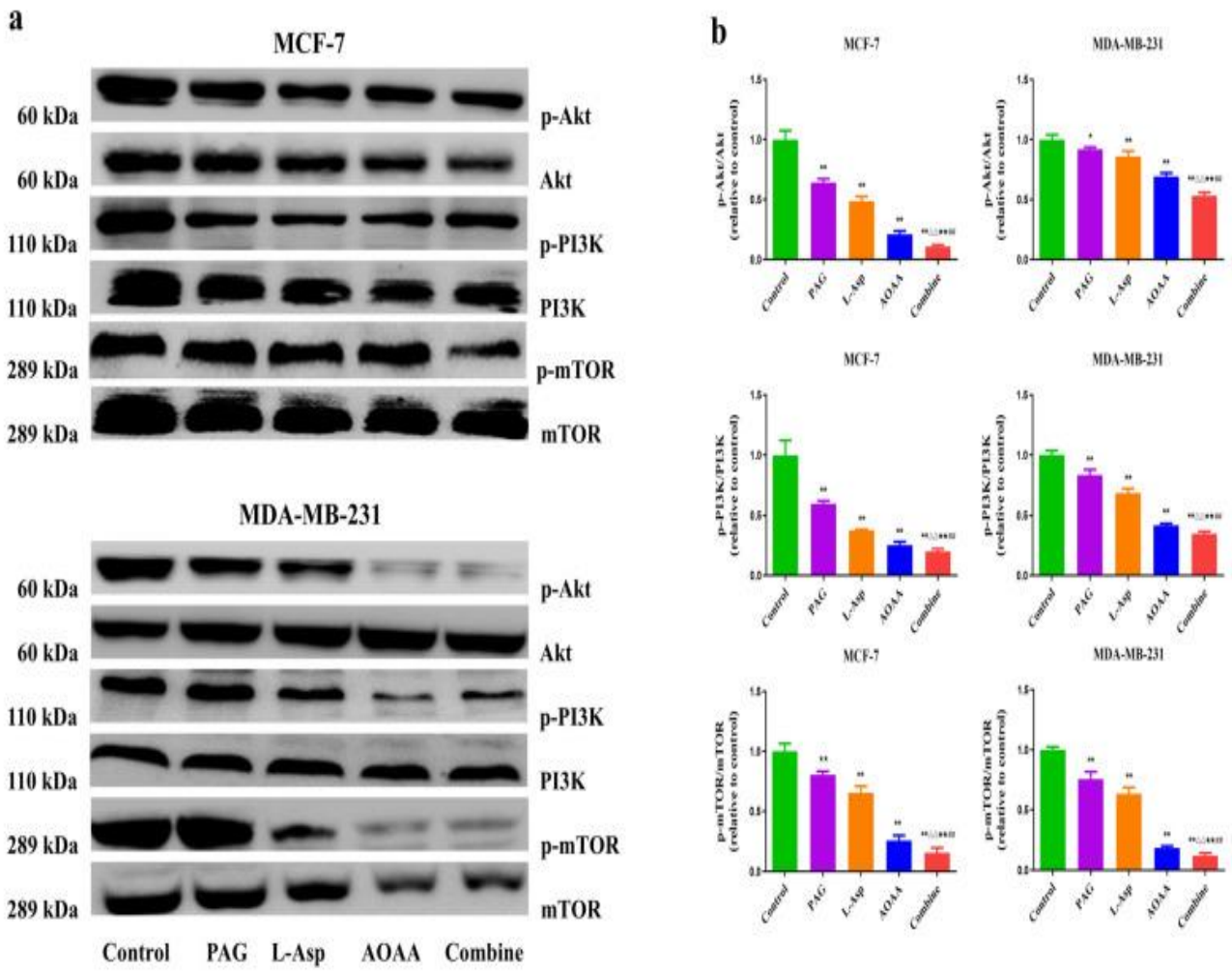
These agents have been well evaluated in different experimental in addition to clinical studies in the form of probable future anticancer treatments [13,14]. Nevertheless, there is no availability of any study with regard to pharmacologic hampering of H2S in BC cells with the utilization of these hampering agents.

Thus Khan etal. [15], performed assessment of pharmacologic hampering of CSE, 3-MPST, as well as CBS which had not been evaluated earlier. Here they studied PAG, L-Asp along with AOAA hampering agents of CSE, 3-MPST, as well as CBS respectively for estimating the part of the endogenous H2S in the growth of BC by in vitro as well as in vivo experiments. An in-silico study was further conducted for corroborating the outcomes obtained. Correlating with every enzyme in different groups they evaluated BC cells (MCF7 along with MDA-MB-231) with10mM of PAG, AOAA along with L-Asp for24h. Observations displayed that combined dosage group (PAG, AOAA along with L-Asp) group demonstrated hampering actions over BC's viability, proliferation, migration in addition to invasion in contrast to group (see Fig1).



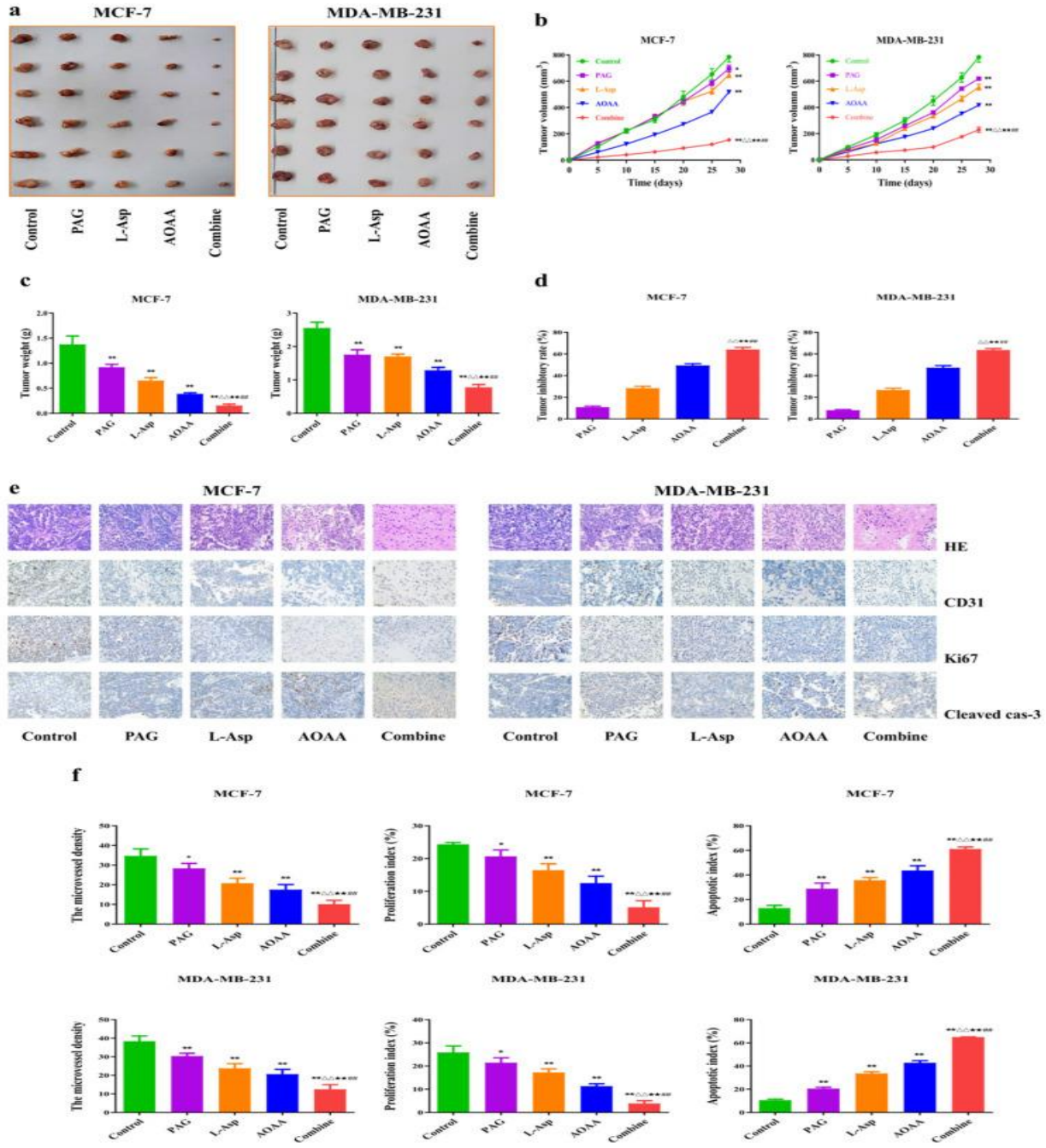
Courtesy ref no-Effects of PAG, AOAA, and L-Asp on the migration and invasion of human BC cells. (**a**) Cell migration was measured by wound-healing assay (original magnification ×100). (**b**) The number of the migrated cells was calculated. (**c**,**d**) Transwell assay was performed to assess the migration and invasion of BC cells (original magnification ×200). (**e**,**f**) The number of the migrated and invasive cells was calculated. The experiments were performed in triplicate. Data are presented as mean ± SEM. ** $p < 0.01$ compared with the control group; △△ $p < 0.01$ compared with PAG group; ★★ $p < 0.01$ compared with AOAA group; ## $p < 0.01$ compared with L-Asp group.

Furthermore, cells which got treatment illustrated escalated apoptosis along with diminished quantities of phosphor(p) extracellular signal – regulated kinase (ERK) for instance -p- protein kinase B(p-AKT)/, p-phosphatidyl inositol 3 - kinase(p-PI3K), mammalian target of rapamycin inhibitors (p-mTOR) (see figure2).



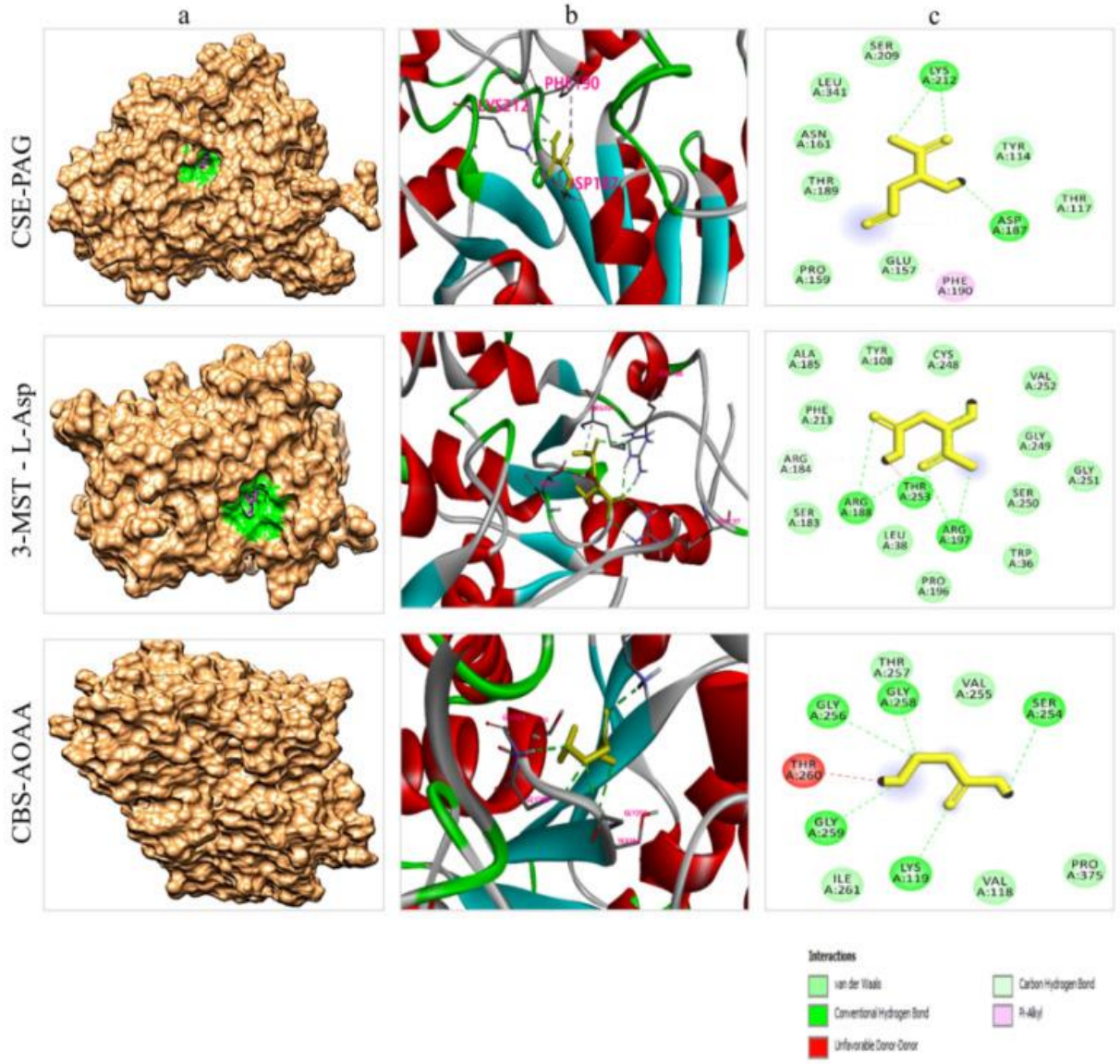
Courtesy ref no-Effects of PAG, AOAA, and L-Asp on the PI3K/AKT/mTOR signaling pathway in human BC cells. (**a**) The expression levels of p-PI3K, p-AKT, and p-mTOR were detected by Western blot. (**b**) Densitometric quantification was performed, normalized to the level of respective non-phosphorylated candidate protein. The experiments were performed in triplicate. Data are presented as mean ± SEM. * $p < 0.05$, ** $p < 0.01$ compared with the control group; △ $p < 0.05$, △△ $p < 0.01$ compared with PAG group; ★ $p < 0.05$, ★★ $p < 0.01$ compared with AOAA group; **##** $p < 0.01$ compared with L-Asp group.

Additionally, the combined dosage group displayed robust hampering actions on the growth of BC xenograft tumors in nude mice without clearcut toxicity (see figure3).



Courtesy ref no-Effects of PAG, AOAA, and L-Asp on the growth of human BC xenograft tumors in nude mice. (**a**) The representative tumor samples from each group are shown. (**b**) The tumor volumes of human BC xenograft tumors were measured ($n = 6$). (**c**) The tumors were weighed ($n = 6$). (**d**) The inhibition rate of tumor growth was calculated ($n = 6$). (**e**) Representative photographs of HE, CD31, Ki67, and cleaved caspase-3 staining in human BC xenograft tumors (original magnification ×400). (**f**) The PI, MVD, and apoptotic index were calculated ($n = 3$). Data are presented as mean ± SEM. * $p < 0.05$, ** $p < 0.01$ compared with the control group; △ $p < 0.05$, △△ $p < 0.01$ compared with PAG group; ★★ $p < 0.01$ compared with AOAA group; ## $p < 0.01$ compared with L-Asp group.

The molecular docking experiments were in agreement- with wet lab experiment in addition to the escalated dependability of these agents (see figure4).



Courtesy ref no-Visualization of drug–protein interaction after molecular docking (**a**) Depiction of each protein docking interaction pocket (magenta: drug molecule, green: drug pocket area in the corresponding enzymes). Note: In the CBS-AOAA complex, the pocket cannot be seen because the drug interaction area is in the cleft of the protein. (**b**) The 3D interaction sites of drugs with corresponding enzymes. (**c**) The 2D interaction of the interacting amino acid residues of the proteins with each drug molecule.

Thus Khan etal. [15], concluded that the outcomes obtained displayed robust hampering actions on the endogenous H2S generation, might significantly hamper the growth of human breast cancer cells through AKT/ PI3K/ mTOR pathway, implying that endogenous H2S might be working in the form of the attractive therapeutic target in case of human breast cancer cells. Their study further gives courage with regard to fashioning innovative H2S dependent anti tumor agents for attaining cure for BC.

Conclusions

Earlier we had reviewed the detailed etiopathogenesis, treatment of BC, where we highlighted the role of H2S; how high amounts of exogenous H2S released from donors repress the growth of different tumors through stimulation of cellular acidification in addition to modulation of different signaling pathways implicated in cell cycle control, proliferation, apoptosis along with metastasis. The selective liberation of some amounts of H2S fromH2S donors in the target has been believed to work as an alternative tumor therapy strategy besides update on management of triple negative breast cancer along with how dysregulated cholesterol metabolism including oxysterols were implicated in the pathophysiology of Breast Cancer along with use that pathway for treating it [16-19].Here we have further extended it by pharmacologic hampering of enzymes like targeting enzymes CSE, 3-MPST, as well as CBS implicated in generation of H2S.

Furthermore, Oza etal. [21], reviewed Nitric oxide (NO), Hydrogen Sulfide (H2S), along with carbon monoxide (CO); how each of them possessed double actions of every gas in variable processes that take place at the time of cancer propagation. NO, H2S, along with CO portray endogenously generated gases with significant working actions in the vasculature, immune defense in addition to inflammation. It has been escalatingly evident that these 3 do not work alone by themselves their actions are getting impacted by modulating actions of each other. Every gas gets generated by 3 enzymes which possess certain tissue specificities

in addition to further possess the capacity of getting generated by nonenzymatically generated by redox reactions different substrates. NO as well as CO share akin characteristics for instance activating soluble guanylate cyclase(sGC) in escalating cyclic guanosine monophosphate(cGMP) quantities. Simultaneously, H2S hampers both phosphodiesterase 5A (PDE 5A), an enzyme having the capacity of controlling sGC along with influencing redox controlling ons GC. The part of NO, H2S, along with CO in the scenario of cancer proliferation along with has been quite confusing, in view of proof for both tumor facilitating as well as pro inflammatory actions in addition to anti-tumor as well as anti-inflammatory actions is present. Every gasotransmitter has been observed to possess double actions with regard to different perspectives over cancer biology inclusive of cancer cell proliferation along with apoptosis, invasion in addition to metastasis, angiogenesis as well as immunomodulation. Such apparently controversial effects might correlate with every gas basedover its local flux. Thus, Oza etal.[21], detailed the main part of NO, H2S, along with CO with regard to cancer for emphasizing the double actions of every gas in variable processes that take place at the time of cancer propagation.

Further Xiang et.al. [22], illustrated how CSE might work in the form of a prognostic biomarker with regard to Hepatocellular carcinoma (HCC) as well as correlated with immune infiltrates.

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