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ABSTRACT

As part of our research group continuous efforts to find alternative treatments for cancer, the aqueous ethanol extracts of fifty-six plants collected from Egypt were screened in vitro for their antileukemic activity against leukemia K562 cell line (Fig.1 and 2). Sesbania sesban L. Merr. (SS; Egyptian riverhemp) was one of the active plants that were selected for further chemical and biological investigations. Bio-guided fractionation of SS leaves hydroethanolic extract resulted in isolation of one undescribed compound (33) (Hederatriol 3-O-β-D-glucuronic acid methyl ester) as well as thirty-four known compounds. Seven compounds (34, 22, 20, 24, 21, 19, 35) showed high anti-proliferative effect (IC50 = 22.3, 30.8, 31.3, 33.7, 36.6, 37.5, 41.5 µM, respectively), while four compounds (32, 5, 29, 1) showed milder activity with (IC50 = 56.4, 67.6, 83.3, 112.3 µM, respectively). A mechanistic study was further carried out on a molecular genetics level against several transcription factors signaling pathways that are incorporated in the incidence of cancer. The results showed that compounds (22, 21) demonstrated specific inhibition of Wnt pathway (IC50 = 3.8, 4.6 µM, respectively), while compound (22) showed specific inhibition of Smad pathway (IC50 = 3.8 µM). Compound (34) was shown to strongly altered the signaling pathways of Smad and E2F (IC50 = 5 µM) (Fig.3). The bioactive metabolites were furtherly investigated in silico by docking against several targets related to K562 cell line. The results showed that compounds 22 and 34 exhibited a strong binding affinity towards topoisomerase (docking score = -7.8056 and -9.2972 Kcal/Mole, respectively) (Fig.4). Compounds 22 and 34 demonstrated strong binding affinity towards EGFR-Tyrosine kinase (docking score = -7.1200, and -7.350 Kcal/Mole, respectively). Moreover, compound 34 showed a strong binding affinity towards Abl kinase (docking score = -7.0463 Kcal/Mole).

ANTILEUKEMIC ACTIVITY

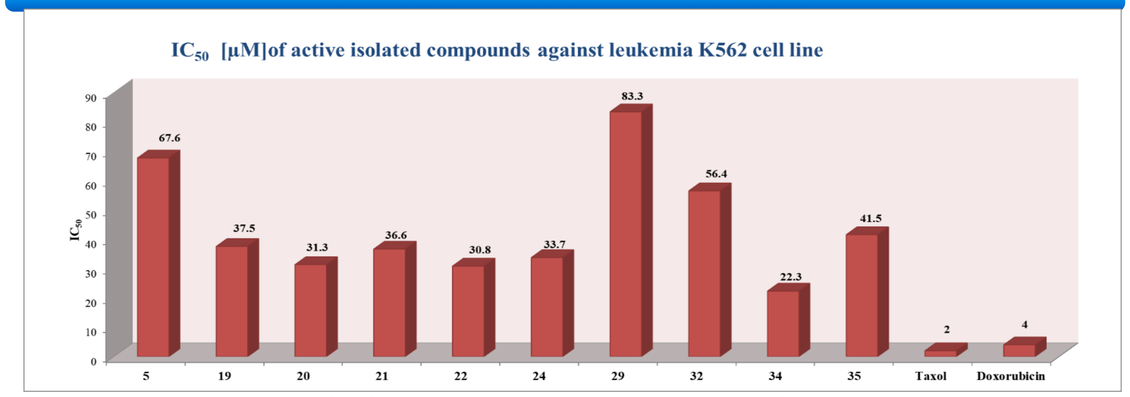


Fig. 1. IC_{50} [µM] of the active isolated compounds against leukemia K562 cell line

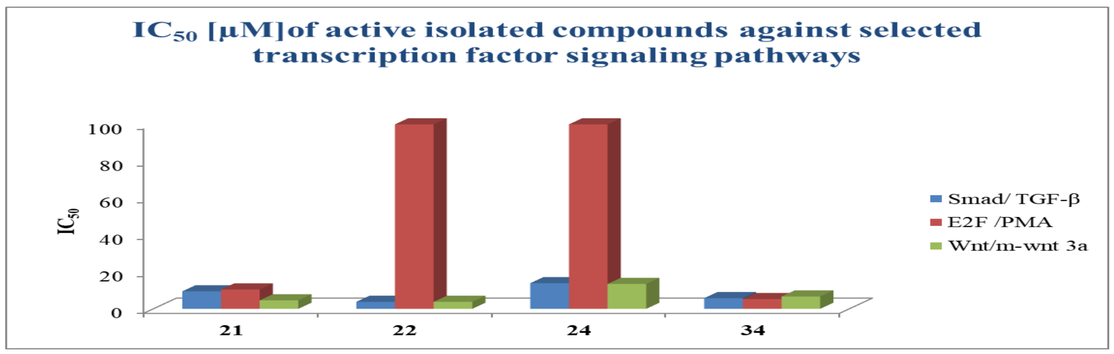


Fig. 2. IC_{50} [µM] of active isolated compounds against selectedtranscription factor signaling pathways

PROPOSED MECHANISM OF ACTION

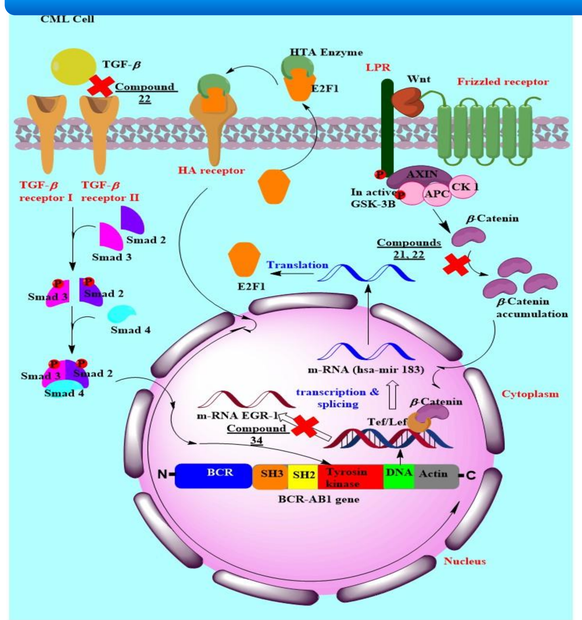
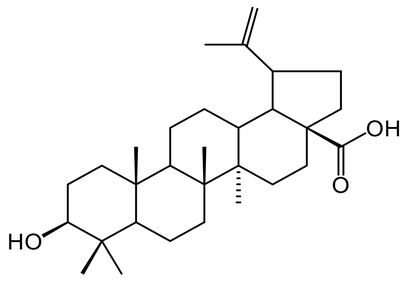


Fig.3. Mode of action of active isolated compounds against; Smad, Wnt and E2F Signaling pathways

The antileukemic activities of these compounds could mainly attributed to targeting the two transcription factors signaling pathways; Smad and Wnt that were previously reported to be incorporated in the incidence and pathogenesis of Leukemia. 3*β*-*O*-(*cis*-*p*-Coumaroyl)-2*α*-hydroxyurs-12-en-28-oic acid (21), Jacoumaric acid (22) showed specific inhibition of Wnt pathway though stimulation of β-catenin degradation and preventing its accumulation while Jacoumaric acid (22) and Oleanolic acid 3-*O*-*β*-D-glucuronopyranoside (34) showed specific inhibition of Smad signaling pathways by acting as antagonists of TGF-β1 binding to its receptor (Fig.3).

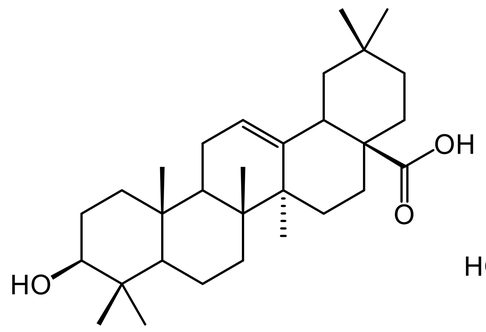
MOLECULAR DOCKING AND SAR

Lupane triterpenoid
Betulinic acid (19)



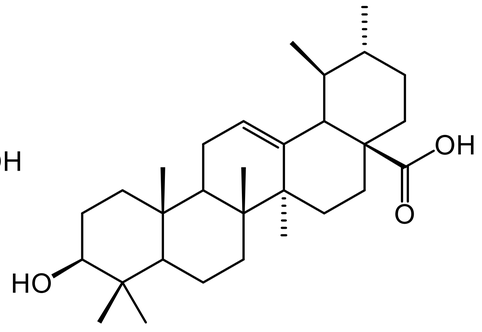
IC_{50} = 37.5 µm

Oleane triterpenoid
Oleanolic acid (5)



IC_{50} = 67.6 µm

Ursane triterpenoid
Ursolic acid (20)



IC_{50} = 31.3 µm

Fig. 4. SAR of different types of triterpenes

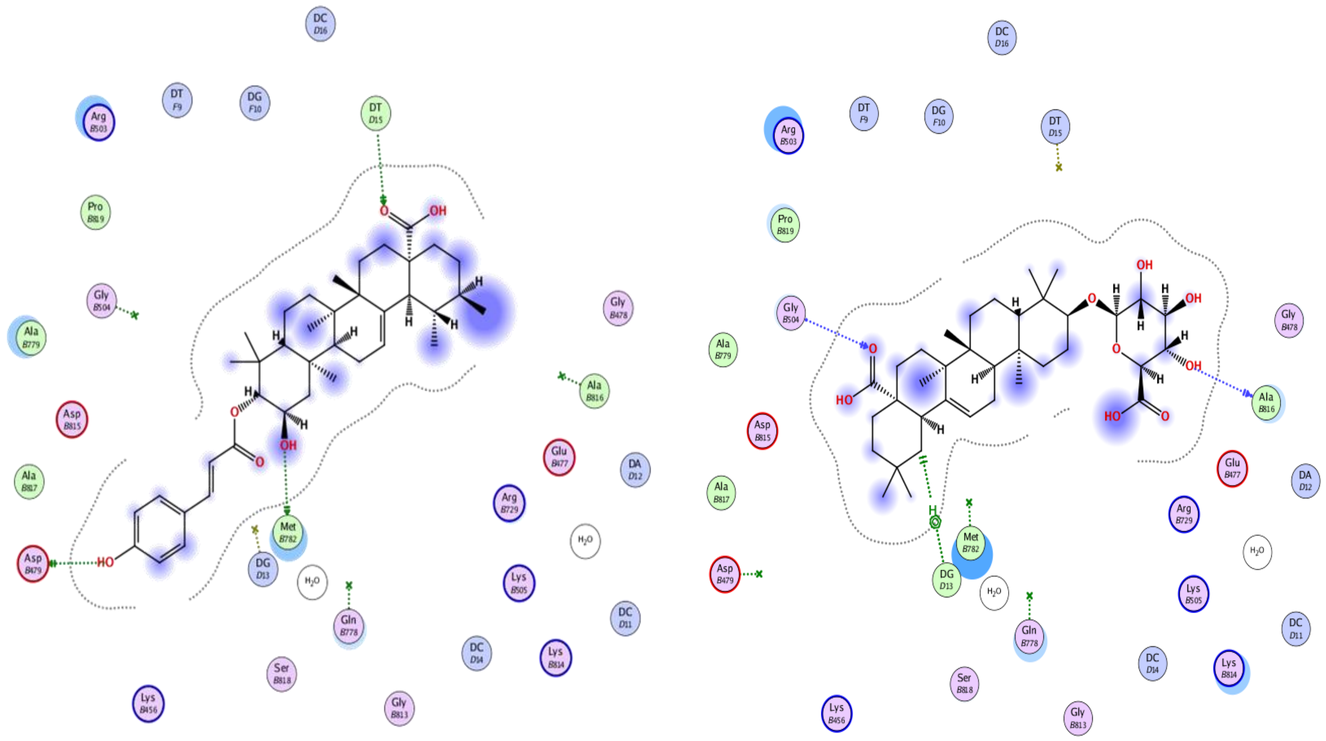


Fig. 5. Docking of compounds 22 and 34 with topoisomerase

CONCLUSIONS

One new compound (33), in addition to thirty-four known compounds were isolated from the leaves of Sesbania sesban encompassing nineteen triterpenoids (3-7, 19-24, 26, 29-35), three steroids (2, 8, 25), eleven flavonoid glycosides (10-18, 27-28), one fatty alcohol (1) and one phenolic compound (9). Thirty of them (1, 3-4, 6-18, 20-33, 35) are reported for the first time from this species. The antileukemic activity of the isolated compounds was evaluated against leukemia K562 cell line in vitro and eleven triterpenoids exhibited a remarkable antileukemic activity against this cell line. Compounds 34 (Oleanolic acid 3-O-β-D-glucuronopyranoside) and 22 (Jacoumaric acid) exhibited the strongest activity with an IC50 value of 22.3, 30.8 µM, respectively.

ACKNOWLEDGMENTS

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