**Objectives**: Opportunistic filamentous fungi are responsible for severe and often fatal infections, especially in immunocompromised individuals. With the limited number of effective antifungals and increasing resistance, drug repurposing emerges as a promising strategy. This study aimed to evaluate the antifungal potential and mechanisms of action of auranofin and iodoquinol, two repurposed drugs, against critical fungal pathogens from the WHO priority list.

**Materials & Methods**: Eight clinically relevant filamentous fungi, including *Aspergillus fumigatus*, *Fusarium oxysporum*, *Scedosporium boydii*, *Lomentospora prolificans*, *Rhizopus oryzae*, *Mucor velutinosus* and *Cunninghamella* sp., were tested. Broth microdilution assays determined MIC70 and MFC values. Additional experiments assessed fungal growth kinetics, effects on preformed biofilms, stressor susceptibility (SDS, NaCl, menadione), cellular alterations via fluorescent staining, and drug interaction profiles using FICI method and Bliss independence models.

**Results**: Auranofin and iodoquinol displayed antifungal activity against all tested species, with MIC70 values ranging from 5µM to >40µM for auranofin and 0.625µM to >40µM for iodoquinol. Growth kinetics revealed that both drugs significantly delayed or suppressed fungal growth over 24 hours, particularly against *L. prolificans*, *S. boydii*, and *A. flavus*. Regarding biofilms, both drugs reduced biomass and metabolic activity, with auranofin achieving up to 90% reduction in *L. prolificans* and iodoquinol showing strong effects on *R. oryzae* and *Cunninghamella* sp. Under stress conditions, auranofin enhanced fungal susceptibility to SDS and menadione, consistent with its known redox interference, while iodoquinol showed selective enhancement under oxidative and osmotic stress in some species. Fluorescence assays demonstrated that both drugs disrupted key cell components—neutral lipids, mannose residues, and chitin—in a species-specific manner. Notably, *A. fumigatus*, *F. oxysporum*, and *R. oryzae* showed marked cellular alterations in the presence of both compounds. The drug interaction studies revealed species-specific synergistic and additive effects when auranofin or iodoquinol were combined with conventional antifungal agents. According to the FICI analysis, iodoquinol exhibited a synergistic interaction with voriconazole against *A. fumigatus*, while the combination with auranofin and voriconazole produced an additive effect. For *F. oxysporum* and *L. prolificans*, both auranofin and iodoquinol combined with voriconazole showed additive effects. In the case of *R. oryzae*, no interaction was observed with posaconazole; however, both compounds demonstrated additive effects when combined with amphotericin B. The Bliss independence model supported these findings and further demonstrated synergistic interactions between voriconazole and both auranofin and iodoquinol against *A. fumigatus*, *F. oxysporum*, and *L. prolificans*. For *R. oryzae*, an antagonistic effect was observed when either auranofin or iodoquinol was combined with posaconazole, while synergistic effects were confirmed when both were combined with amphotericin B.

**Conclusion**: Auranofin and iodoquinol demonstrate broad-spectrum antifungal activity against high-priority filamentous fungi, including strains with known antifungal resistance. Their effects on biofilms, stress response, and cellular integrity highlight their potential for repurposing as antifungal agents. Moreover, the observed synergistic interactions with existing antifungals suggest their potential use in combination therapies. These findings support further preclinical development and mechanistic studies of auranofin and iodoquinol as novel therapeutic alternatives for refractory fungal infections.