**Supplementary Table S10** Targets and potency-enhancing molecular interaction modes in 5 fully sub-potent natural product combinations with potencies of a non-principal component increased by 10-100 fold

| Ingredient | Role in Combination | Dose Reduction Index | Target, Therapeutic Effect or Response (reference in Pubmed ID) | Effect type | Potency-Enhancing Synergistic Modes (reference in Pubmed ID) | Synergism Type |
|---|---|---|---|---|---|---|
| **Combination 1** | | | | | | |
| **Vanillin (0.6mg/mL)** | **Principal therapeutic ingredient** | 8 | inhibited CYP53A15 to produce antifungal effect (18505250) | Antifungal | (+/-)-pinoresinol caused damage to fungal plasma membrane(20657496) to enhance vanillin's transport across fungal membrane (15868144) | Intracellular bioavailability enhancement |
| | | | polymerized by laccase lacA to reduce its antifungal effect | Counteractive action | | |
| | | | catabolized by vanillin dehydrogenase vdh (22057861) | Counteractive action | | |
| | | | | | | |
| 4-hydroxy-3-methoxycinnamaldehyde (0.4mg/mL) | Cooperative | 2 | antifungal mechanism unreported | | | |
| | | | | | | |
| (+/-)-pinoresinol (1mg/mL) | Cooperative | 10 | caused damage to | Antifungal | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | fungal plasma membrane to produce antifungal effect (20657496) | | | |
| | | | | | | |
| **Combination 2** | | | | | | |
| **Vanillin (0.6mg/mL)** | **Principal therapeutic ingredient** | 3 | inhibited CYP53A15 to produce antifungal effect (18505250) | Antifungal | Scopoletin inhibited fungal efflux pumps (15826040) | Intracellular bioavailability enhancement |
| | | | polymerized by laccase lacA to reduce its antifungal effect | Counteractive action | | |
| | | | catabolized by vanillin dehydrogenase vdh (22057861) | Counteractive action | Scopoletin inhibited fungal oxidation of vanillin to enhance its bioavailability (15826040) | Intracellular bioavailability enhancement |
| | | | | | | |
| 4-Hydroxy-3-methoxycinnamaldehyde (0.4mg/mL) | Cooperative | 4 | antifungal mechanism unreported | | | |
| | | | | | | |
| Scopoletin (1.5mg/mL) | Cooperative | 18.8 | hindered fungi survival or germination, inhibited detoxification enzymes (15826040) | Antifungal | | |
| | | | | | | |
| **Combination 3** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **berberine (125ug/mL)** | **Principal therapeutic ingredient** | 4.2 | inhibited microbial division protein FtsZ to produce antimicrobial effect (18275156, 21060782) | antimicrobial | | |
| | | | effluxed by a multidrug pump (10677479) | Efflux-mediated multidrug resistance | chrysosplenol-D inhibited the mutidrug pump, thereby potentiated berberine's antimicrobial activity (12494348) | Intracellular bioavailability enhancement |
| | | | | | | |
| chrysosplenol-D (250ug/mL) | Cooperative | 10 | antimicrobial mechanism unreported | | | |
| | | | | | | |
| **Combination 4** | | | | | | |
| **berberine (125ug/mL)** | **Principal therapeutic ingredient** | 4.2 | inhibited microbial division protein FtsZ to produce antimicrobial effect (18275156, 21060782) | antimicrobial | | |
| | | | effluxed by a multidrug pump (10677479) | Efflux-mediated multidrug resistance | chrysoplenetin inhibited the mutidrug pump, thereby potentiated berberine's antimicrobial activity (12494348) | Intracellular bioavailability enhancement |
| | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| chrysoplenetin (250ug/mL) | Cooperative | 40 | antimicrobial mechanism unreported | | | |
| | | | | | | |
| **Combination 5** | | | | | | |
| **curcumin (3.1uM)** | **Principal therapeutic ingredient** | 3.1 | downregulated Notch1 and Bcl-xL to inactivate NFkB, thereby promoting growth inhibition and apoptosis (16628653) | Anticancer, growth inhibition, apoptosis | isoflavone inhibited Notch, NFkB and AkT, and activated P53(22200028) to complement curcumin's action on Notch1 and Bcl-xL (16628653), thereby further promoting apoptosis | Complementary action |
| | | | activated P38, thereby downregulating Bcl2, survivin and AkT signaling to promote apoptosis (19676105) | Anticancer, apoptosis | isoflavone inhibited Notch, NFkB and AkT, and activated P53(22200028) to complement curcumin's action on Bcl2, survivin and AkT (19676105), thereby further promoting apoptosis | Complementary action |
| | | | inhibited AKT-mTOR pathway to promote anticancer effect (21450334 ) | Anticancer, growth inhibition | | |
| | | | | | | |
| isoflavone (183uM) | Cooperative | 18.3 | inhibited Notch, NFkB and AkT, and activated P53 to promote | Anticancer, apoptosis | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | apoptosis (22200028) | | | |