



# Mithridates VI Eupator, father of the empirical toxicology

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## LETTER TO THE EDITOR

### Mithridates VI Eupator, father of the empirical toxicology

*To the Editor:*

We read with pleasure the article by Gunduz et al., titled "Clinical review of grayanotoxin/mad honey poisoning past and present,"<sup>1</sup> that offers an overview of the toxicological aspects of the "mad honey." However, from a historical point of view and in a toxicological context, an observation seems mandatory. The king of Pontus (in northeast Anatolia), whose allies used grayanotoxin-containing honey against the troops of Pompey the Great, was Mithridates VI Eupator (132–63 BC), not Mithridates IV Philopator Philadelphus, who died circa 150 BC (more than 80 years before the Roman conquest of Pontus) and brother of the grandfather of Mithridates VI.

The mistake probably reflects the fact that in ancient Middle East, many kings bore the name "Mithridates"<sup>2–4</sup> and should be corrected because Mithridates VI Eupator king of Pontus was one of the pioneers of clinical toxicology.<sup>5</sup>

Mithridates VI was the author of a book on roots and plants<sup>6</sup> that at those times were one of the most important sources on venoms, which he used to secretly kill his enemies.<sup>7</sup> The interest of Mithridates VI in empirical clinical toxicology is also demonstrated by the experiments that he carried out on prisoners condemned to capital punishment to test poisons and antidotes.<sup>8</sup>

Moreover, as he was afraid to be poisoned, he started to protect himself against poisons by taking progressively increasing sublethal doses. The chemical toxicology of them is unknown but there probably was no additive effect. In this way, Mithridates VI acquired resistance to poisoning possibly by enzymatic activation or metabolic functional changes (mithridatism). This, paradoxically, resulted in an unwanted effect: when he understood that he was falling in his enemies' hands, he attempted to commit suicide, but because of his acquired tolerance, the amount of poison he swallowed did not kill him despite the fact that he walked around rapidly to hasten its action.<sup>9</sup> Consequently, he looked for death by sword.<sup>9,10</sup>

Besides mithridatism, Mithridates VI gave the name to "mithridatum," a general antidote whose recipe was found in his cabinet by Roman soldiers and carried to Rome by Pompey. Despite Pliny's criticism,<sup>11</sup> the

"mithridatum", with some modifications, was given the name "theriaca" and used in medicine until the nineteenth century.<sup>12</sup>

The intentional use of mad honey to overwhelm enemy forces is one of the first recorded uses of a biotoxin in warfare and is perfectly correspondent to the personality and to the scientific interests of Mithridates VI Eupator king of Pontus.

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