

The COC Protocol – How It Works

Reported anticancer mechanism*	COC Protocol Medication	Refs
Reduces availability of nutrients to cancer cells (e.g. glucose, fats, and glutamine)	Metformin, Statin	Metformin (Rosilio et al., 2014; Saladini et al., 2019) Statins (Babcook et al., 2016)
Stimulates and facilitates anti-cancer immune response	Statin, Mebendazole, Metformin, Doxycycline	Statin (Al Dujaily et al., 2020; Al-Husein et al., 2018; Yongjun et al., 2013) Mebendazole (Blom et al., 2017; Guerini et al., 2019) Metformin (Bahrambeigi and Shafiei-Irannejad, 2019; Eikawa et al., 2015; Kurelac et al., 2019; Pereira et al., 2018) Doxycycline (Lucero-Diaz et al., 2016; Tang et al., 2013, 2017)
Places cancer cells under 'metabolic stress'	Metformin, Statin, Doxycycline	Metformin reviewed in (Pernicova and Korbonits, 2014; Tronccone et al., 2017) Statin (Clendening and Penn, 2012; Huang et al., 2020; McGregor et al., 2020; Urbano et al., 2017) Doxycycline (De Francesco et al., 2017; Petóvári et al., 2018; Tan et al., 2017)
Modulates mitochondrial function in cancer cells	Doxycycline, Metformin	Doxycycline (Lamb et al., 2015a; Ozsvári et al., 2017) Metformin reviewed in (Cazzaniga and Bonanni, 2015)
Disrupts cancer cell growth and migration	Metformin, Statin, Mebendazole, Doxycycline	Statin reviewed in (Altwairgi, 2015) Metformin reviewed in (Chae et al., 2016; Jang et al., 2014; Seliger et al., 2016) Mebendazole (Mukhopadhyay et al., 2002; Pinto et al., 2015) Doxycycline (Fife and Sledge, 1995; Wang et al., 2015; Yang et al., 2015)
Induces programmed cancer cell death (apoptosis)	Metformin, Statin, Mebendazole, Doxycycline	Doxycycline (Fife et al., 1998; Onoda et al., 2006; Son et al., 2009; Song et al., 2014) Mebendazole (Doudican et al., 2008; Mukhopadhyay et al., 2002; Sasaki et al., 2002) Statin (Bayat et al., 2016; Cafforio et al., 2005; Fromigué et al., 2006) Metformin (Gu et al., 2015; Kalinsky et al., 2017; Kumar et al., 2014; Yousef and Tsiani, 2017)
Blocks cancer cell DNA damage repair	Doxycycline, Mebendazole	Doxycycline (Lamb et al., 2015b; Peiris-Pagès et al., 2015) Mebendazole (Markowitz et al., 2017), also reviewed in (Guerini et al., 2019)
Slows growth of tumor-feeding blood vessels (anti-angiogenic activity)	Mebendazole, Metformin	Mebendazole (Bai et al., 2015), also reviewed in (Guerini et al., 2019) Metformin (Orecchioni et al., 2015; Qian et al., 2018)
Targets cancer stem cells and may help make them more vulnerable to standard cancer treatments	Metformin, Statin, Doxycycline	Metformin (Bao et al., 2014; Brown et al., 2020; Hirsch et al., 2009) Doxycycline (Lamb et al., 2015a; Lin et al., 2018; Scatena et al., 2018; Yang et al., 2015) Statin (Afzali et al., 2016; Bayat et al., 2016; Kato et al., 2018; Kodach et al., 2011; Li et al., 2017; Peng et al., 2017)

